Proposed Registration Decision PRD2016-07

Buprofezin

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Overview

Proposed Registration Decision for Buprofezin

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Buprofezin Technical and Applaud Insect Growth Regulator, containing the technical grade active ingredient buprofezin, to control whiteflies on greenhouse vegetables (cucumbers, peppers and tomatoes) and greenhouse ornamentals (excluding cut flowers).

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of Buprofezin and Applaud Insect Growth Regulator.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment. These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

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1 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

2 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "... the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

Before making a final registration decision on buprofezin, the PMRA will consider any comments received from the public in response to this consultation document.[3] The PMRA will then publish a Registration Decision[4] on buprofezin, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

What Is Buprofezin?

Buprofezin is an insect growth regulator that is effective against insects that suck plant sap, such as whiteflies. Buprofezin is the active ingredient in Applaud Insect Growth Regulator, which controls whiteflies when applied to the foliage of greenhouse vegetables (cucumbers, peppers and tomatoes) and greenhouse ornamentals (excluding cut flowers). Applaud Insect Growth Regulator is effective against larval stages of whiteflies, and also affects the ability of adults to produce viable eggs.

Health Considerations

Can Approved Uses of Buprofezin Affect Human Health?

Applaud Insect Growth Regulator, containing buprofezin, is unlikely to affect your health when used according to label directions.

Potential exposure to buprofezin may occur through the diet (food and water), when handling and applying the product, or during contact with treated surfaces. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when pesticide products are used according to label directions.

In laboratory animals, buprofezin was of low acute toxicity via the oral, dermal, and inhalation routes of exposure, was minimally irritating to the eyes and non-irritating to the skin, and did not cause an allergic skin reaction.

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3 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

4 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

The end-use product Applaud Insect Growth Regulator, containing buprofezin, was of low acute toxicity by the oral, dermal, and inhalation routes of exposure, was mildly irritating to the eyes and slightly irritating to the skin, and did not cause an allergic skin reaction.

Registrant-supplied short, and long term (lifetime) animal toxicity tests, as well as information from the published scientific literature were assessed for the potential of buprofezin to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The most sensitive endpoints for risk assessment included effects on the liver and thyroid gland, as well as lack of coordinated movement. In addition, there was evidence that young animals were more sensitive than adult animals to buprofezin toxicity as demonstrated by reduced offspring body weight and effects on the thyroid gland at a dose that was not harmful to the maternal animal. Longer-term dosing with buprofezin resulted in liver tumors in mice, but not in rats. The risk assessment protects against the effects noted above and any other potential effects by ensuring that the level of exposure to humans is well below the lowest dose at which these effects occurred in test animals.

Residues in Water and Food

Dietary risks from food and drinking water are not of health concern.

Dietary intake estimates (food alone) revealed that the general population and all subpopulations are expected to be exposed to less than 8% of the acceptable daily intake. Dietary intake estimates from food plus drinking water was not conducted since there is no expectation of buprofezin residues in drinking water from the proposed uses (i.e. greenhouse and imported crops). Based on these estimates, the chronic dietary risk from buprofezin is not a health concern for all population subgroups. The lifetime cancer risk from the use of buprofezin on the crops assessed is also not of health concern.

Acute dietary intake estimates for the general population and all population subgroups was less than 48% of the acute reference dose, and are not of health concern.

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

Residue trials conducted throughout Canada and the United States using buprofezin on all petitioned crops are acceptable. The MRLs for this active ingredient can be found in the Science Evaluation section of this document.

Risks in Residential and Other Non-Occupational Environments

The use pattern for Applaud Insect Growth Regulator is limited to greenhouses, therefore, risks to people in residential and other non-occupational environments is expected to be negligible.

Occupational Risks From Handling Applaud Insect Growth Regulator

Occupational risks are not of concern when Applaud Insect Growth Regulator is used according to the proposed label directions, which include protective measures such as personal protective equipment, restricted-entry intervals and an extended retreatment interval.

Farmers and custom applicators who mix, load or apply Applaud Insect Growth Regulator as well as workers re-entering treated greenhouses can come in direct contact with buprofezin residues on the skin and/or through inhalation. Therefore, the label specifies that workers must wear a long-sleeved shirt, long pants, chemical resistant gloves and shoes plus socks during mixing, loading, application, clean up and repair. It is also required that workers not enter treated greenhouses for 12 hours after application to ornamentals (excluding cut flowers), ground covers, and/or landscape plants and for 2 days after application to greenhouse cucumbers, tomatoes and peppers. Taking into consideration these label statements, the number of applications and the duration of exposure for mixer/loader/applicators and re-entry workers, the risk to these individuals are not a concern.

For bystanders, exposure is expected to be much less than that for workers and is considered negligible. Therefore, health risks to bystanders are not of concern.

Environmental Considerations

What Happens When Buprofezin Is Introduced Into the Environment?

When used according to label direction buprofezin is not expected to pose an unacceptable risk to the environment.

Because buprofezin is proposed for use in greenhouses, environmental exposure is expected to be limited. When buprofezin is sprayed onto tomatoes, peppers and cucumbers in a greenhouse, any buprofezin that volatilizes into the air is quickly degraded upon exposure to light. Any buprofezin that ends up on soil is broken down by soil microbes and will not persist in soil.

Buprofezin is not expected to have any harmful effects on bees or beneficial arthropods that are used in greenhouses.

Buprofezin can enter surface waters if run-off effluent is released from the greenhouse. Once in surface water, buprofezin will break down in water but it can also bind to sediment and suspended organic matter. When it binds to sediment it can accumulate and gradually break down. If buprofezin enters surface water at high enough levels, it could pose a risk to aquatic organisms and could accumulate in fish, but the levels anticipated for the proposed use pattern are relatively low and buprofezin is not expected to pose an unacceptable risk.

Value Considerations

What Is the Value of Applaud Insect Growth Regulator?

Applaud Insect Growth Regulator controls whiteflies on greenhouse vegetables (cucumbers, peppers and tomatoes) and greenhouse ornamentals (excluding cut flowers).

Applaud Insect Growth Regulator has value because it controls whiteflies when sprayed on the foliage of greenhouse cucumbers, peppers, tomatoes and greenhouse ornamentals (excluding cut flowers). Whiteflies are a major pest in greenhouses and have developed resistance to many of the currently registered insecticides. Because the mode of action of buprofezin is new to Canada, it will contribute to resistance management of whiteflies in greenhouses.

Growers have identified Applaud Insect Growth Regulator as a high priority for control of whiteflies on greenhouse cucumber, pepper, tomato, and ornamentals. Additionally, the product may be used as part of greenhouse integrated pest management programs and is compatible with other greenhouse pest management strategies.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of Applaud Insect Growth Regulator to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

As users can come into direct contact with buprofezin on the skin or through inhalation of spray mists, workers handling Applaud Insect Growth Regulator must wear a long-sleeved shirt, long pants and chemical resistant gloves and shoes plus socks during mixing, loading, application, clean up and repair. To reduce exposure to re-entry workers to buprofezin residues, they are not to enter treated greenhouses for 12 hours after application to greenhouse ornamentals (excluding cut flowers), greenhouse ground covers, and landscape plants grown in greenhouses and for 2 days after application to greenhouse cucumbers, tomatoes and peppers. Based on the results of the dislodgeable foliar residue (DFR) study, the retreatment interval for two applications per crop cycle has been extended to 21 days for vegetables which allows for greater residue dissipation between applications.

Environment

Mitigation statements are required on the Applaud Insect Growth Regulator label to minimize the potential release of greenhouse effluent into the environment.

Next Steps

Before making a final registration decision on buprofezin, the PMRA will consider any comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please note that, to comply with Canada's international trade obligations, consultation on the proposed MRLs will also be conducted internationally via a notification to the World Trade Organization. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

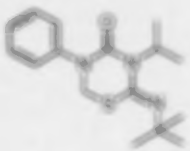
Other Information

When the PMRA makes its registration decision, it will publish a Registration Decision on buprofezin (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Buprofezin

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Buprofezin
Function	Insect Growth Regulator
Chemical name	
1. **International Union of Pure and Applied Chemistry (IUPAC)**	(*Z*)-2-*tert*-butylimino-3-isopropyl-5-phenyl-1,3,5-thiadiazinan-4-one
2. **Chemical Abstracts Service (CAS)**	(*Z*)-2-[(1,1-dimethylethyl)imino]tetrahydro-3-(1-methylethyl)-5-phenyl-4*H*-1,3,5-thiadiazin-4-one
CAS number	953030-84-7
Molecular formula	$C_{16}H_{23}N_3OS$
Molecular weight	305.44
Structural formula	
Purity of the active ingredient	99.29

6.2 Physical and Chemical Properties of the Active Ingredient and End-Use Product

Technical Product – Boprofezin Technical

Property	Result
Colour and physical state	white or light yellow powder
Odour	pungent sulphurous odour
Melting range	109 – 110°C
Boiling point or range	not applicable
Density	1.1868 g/cm³
Vapour pressure at 25°C	8.2 × 10⁻⁷ Pa at 20 °C 1.7 × 10⁻⁶ Pa at 30 °C
Ultraviolet (UV)-visible spectrum	Solution: wavelength of max extinction (nm); coefficient (l/mol × cm) Neutral: 285; 11000 Acidic: 227; 16000 Basic: 285; 11000
Solubility in water at 25°C	0.383 mg/l
Solubility in organic solvents at 20°C	Solvent: Solubility (g/l) Dichloromethane: 987 Chloroform: 520 Toluene: 320 Acetone: 240 Ethyl Acetate: 220 Methanol: 87 n-Octanol: 25 n-Hexane: 20 n-Heptane: 18
n-Octanol-water partition coefficient (K_{ow})	Log K_{ow} : 4.31
Dissociation constant (pK_a)	The active does not ionize or dissociate at environmental pH
Stability (temperature, metal)	Stable at 54 °C for two weeks, stable when exposed to metal (Ni, Cu, Fe, Zn) and aqueous Ni salts, unstable when exposed to aqueous Cu, Fe and Zn salts. Stable under artificial sunlight for two weeks.

End-Use Product – Applaud Insect Growth Regulator

Property	Result
Colour	Tan
Odour	Faint Odor
Physical state	Solid granule material
Formulation type	Dry, Flowable (DF)
Guarantee	70%
Container material and description	HDPE plastic jug
Density	0.29 g/cm^3
pH of 1% dispersion in water	6.3
Oxidizing or reducing action	Not expected to have oxidizing or reducing properties
Storage stability	Stable for over two years in polyethylene lined paper bags
Corrosion characteristics	Not corrosive to the commercial packaging materials
Explosibility	Not considered potentially explosive

6.0 Directions for Use

Applaud Insect Growth Regulator controls whitefly on greenhouse vegetables (cucumber, pepper, and tomato) and greenhouse ornamentals (excluding cut flowers). Applaud Insect Growth Regulator is applied as a foliar spray at 50-83 g product/100 L. The high concentration is for use against high whitefly populations. A maximum of 2 applications per crop cycle, with an application interval of at least 21 days, can be made on the listed greenhouse vegetables. Only one application per crop cycle is allowed for greenhouse ornamentals. For greenhouse vegetables the maximum amount of spray solution that can be applied per hectare is 670 L at the low concentration or 750 L at the high concentration. For greenhouse ornamentals the maximum spray volume is 1000 L per hectare.

6.0 Mode of Action

Buprofezin is an insect growth regulator in Mode of Action Group 16 (inhibition of chitin biosynthesis). During an insect's development, buprofezin interferes with the formation of chitin, which is an essential part of an insect's exoskeleton. As a result, the insect dies before reaching maturity. Buprofezin also suppresses egg development in adult females and reduces viability of eggs. It is particularly effective against certain insects that molt plant-up, such as whiteflies.

7.0 Methods of Analysis

7.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and impurities in the technical product have been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulation Analysis

The method provided for the analysis of the active ingredient in the formulation has been validated and assessed to be acceptable for use as an enforcement analytical method.

2.3 Methods for Residue Analysis

For determination of residues in soil, a gas chromatography - nitrogen / phosphorus detector (GC-NPD) method was developed and proposed for data generation and enforcement purposes. For determination of residues in water, a high-performance liquid chromatography - ultraviolet detector (HPLC-UV) method was developed and proposed for data generation and enforcement purposes. These methods fulfilled the requirements with regards to selectivity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in environmental media. Methods for residue analysis are summarized in Appendix I, Table 1.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

A detailed review of the toxicological database for buprofezin was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. Many studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices (GLP) while some of the older studies were performed prior to the widespread use of GLP. In addition, use was made of results of several toxicology studies reported in other regulatory authority documentation to supplement the assessment. The scientific quality of the data is good and the database is considered adequate to define the majority of the toxic effects that may result from exposure to buprofezin.

Investigation of toxicokinetic parameters in the rat using buprofezin radiolabelled in either the phenol or thiadiazinane ring indicated essentially similar results for males and females. Following single oral gavage low or high dose administration of buprofezin, the maximum concentration in the blood was attained within 9 hours. Distribution of radioactivity to organs occurred within 2 hours of dosing. The highest levels of residual radioactivity occurred in red blood cells, thyroid, kidney and the liver. Buprofezin was rapidly excreted with the majority of the administered dose (AD) excreted by 48 hours with less than 1% of AD remaining in the body after 7 days. Feces accounted for the majority of excreted radiolabel followed by urine. In bile duct-cannulated rats, 24 hours post-dosing, one-third of the AD was recovered in bile with only minor amounts appearing in urine. Excretion via expired air was negligible. Although elimination appeared to be faster in males than females in the first 24 hours, the rates were fairly even by 48 hours post-dosing. The majority of radioactivity in feces was unchanged buprofezin (45% of AD) and metabolites BF27 (7% of AD) and BF28 (5% of AD) along with a number of other metabolites in trace quantities. The urine contained polar conjugates in low concentrations.

The metabolic pathway of buprofezin involved hydroxylation and subsequent methylation of the phenyl ring, oxidation of sulfur with subsequent ring-opening of the thiadiazinane ring and conjugation reactions with sulfate and glucuronic acid. When rats were dosed with buprofezin for 24 weeks there did not appear to be any evidence of accumulation of parent compound in

tissues over time. However, since the analysis was limited to buprofezin, no conclusions as to the metabolite profiles in tissues could be drawn.

Acute toxicity studies with buprofezin identified low toxicity in rats via the oral, dermal and inhalation routes. In rabbits, buprofezin was minimally irritating to the eyes, and non-irritating to the skin. Buprofezin was not a dermal sensitizer in guinea pigs (Buehler method), or in mice (local lymph node assay).

Acute toxicity studies with the end-use product, Applaud Insect Growth Regulator, identified low toxicity in rats via the oral, dermal and inhalation routes. In rabbits, buprofezin was mildly irritating to the eyes, and slightly irritating to the skin. Buprofezin was not a dermal sensitizer in guinea pigs (Buehler method).

Repeat-dose oral studies in mice and rats (dietary administration), and in dogs (capsule administration) identified a decrease in body weight/body weight gain and revealed the liver and/or thyroid as the main target organs. Increased liver weights were noted at the lower dose levels in all species and at higher doses, histopathological changes such as hypertrophy and hyperplasia of the liver were noted in rats and dogs. No thyroid effects were observed in mice; however, thyroid toxicity was noted in rats and dogs as evidenced by increased thyroid weight and an increased incidence of thyroid follicular cell hypertrophy and hyperplasia, as well as a decrease in thyroid hormone serum concentration. The effects on liver and thyroid in rats, which also included induction of cytochrome P450 (CYP2B) and liver microsomal 4NP-UDP-GT, occurred as early as 7 days following initiation of dosing. These changes were accompanied by increases in serum thyroid stimulating hormone (TSH) concentrations, with decreases in T3 levels at higher doses. Additional findings in dogs included observations of ataxia following the first few days of capsule administration. Subdued mood and distended abdomen, as well as increases in prothrombin time were also observed.

There was evidence of increased toxicity with increasing duration of dosing in the database. Bile duct hyperplasia was observed in dogs following long-term dosing only. In rats, thyroid follicular cell hyperplasia was recorded at lower doses in the chronic toxicity/oncogenicity study than those producing this finding in the 90-day study. In addition, reductions in kidney weight were observed in the rat long-term study only.

Following short-term repeated dermal exposure to buprofezin, liver effects consisting of focal necrosis and inflammatory infiltrate were noted in female rats at the limit dose of testing. Systemic toxicity was not observed in males. Dermal irritation was noted in both sexes at the high dose, notably hyperkeratosis in males and dermal inflammatory response in females.

A request from the applicant to waive the requirement for a 90-day inhalation toxicity study was accepted based on low vapour pressure and low acute inhalation toxicity. However, the applicant later provided a 28-day inhalation toxicity study in rats. This study did not identify any new target organs from those identified in repeat-dose oral toxicity studies. The most notable effects in the 28-day inhalation toxicity study were increased adrenal gland weight in females, and increased liver weight as well as hypertrophy of the liver and adrenal gland in both sexes.

Overall, buprofezin did not appear to be genotoxic. Negative results were obtained in a battery of in vitro and in vivo genotoxicity studies, with the exception of positive responses noted at and above the limit dose in the two in vivo mouse micronucleus assays. Information in the scientific

literature also identified an increased incidence of micronuclei formation following in vitro testing. Additional kinetochore analysis conducted in two of the micronucleus assays (one in vitro and one in vivo study) identified an increase in the number of kinetochore positive nuclei, suggesting that buprofezin is not clastogenic, but instead behaves as an aneuploidogen interacting with the mitotic apparatus.

In a two-year dietary chronic/oncogenicity study in rats, a slight but non-statistically significant increase in the incidence of liver adenomas was noted in females in the high dose group when compared to controls. There was no increase in the incidence of carcinomas in females and the tumor response in treated male rats was comparable to controls. For these reasons, the slight increase in incidence of liver adenomas in treated female rats was determined to be of low concern. In a two-year dietary chronic/oncogenicity study in mice, there was no evidence of oncogenicity in males. In females, a statistically significant increase in the incidence of liver adenomas was noted at the two highest dose levels compared to the control group. The incidence of liver carcinomas in treated female mice was comparable to controls. The combined incidence of liver adenomas and carcinomas was statistically significantly increased at the highest dose level. In the absence of a supported mode of action for tumor development, a quantitative linear low dose extrapolation (q_1*) based on the combined incidence of adenoma/carcinomas was deemed appropriate for the cancer risk assessment.

In a two-generation dietary reproduction study in rats, there were no treatment-related adverse effects in parental animals at the highest dose tested. At the same high dose, reductions in offspring body weights, occurring as early as post-natal day (PND) 7, were recorded in the second generation, indicating sensitivity of the young, although this endpoint was not considered serious. There was no impact on reproductive parameters. In an oral gavage developmental toxicity study in rabbits, dams showed decreases in body weight and body weight gain, food consumption and fecal output at the highest dose tested. There was no indication of developmental toxicity. In an oral gavage developmental toxicity study in rats, effects in dams were only observed at the highest dose, a dose level approaching the limit dose of testing. These findings included clinical signs, reductions in body weight and food consumption as well as increases in resorptions, post-implantation loss, and decreased live fetuses. Fetal effects were also only observed at the highest dose level and, in addition to the decrease in live fetuses, included reduced body weights and numerous variations. The results of this study identified a serious effect (fetal death) occurring in the presence of maternal toxicity.

A range-finding study in rats was conducted in order to establish dose levels for a definitive study to investigate thyroid hormone response during fetal neurodevelopment. In this study, dams received buprofezin via oral gavage from gestation day (GD) 6 to lactation day (LD) 6. An additional group of non-pregnant females were dosed in a similar manner for a comparable time period. A subset of the delivered pups were gavage-dosed with the same dose levels as the dams from PND 6-21, with remaining pups untreated for the same duration. Increases in thyroid and liver weights, thyroid follicular cell hypertrophy, and hepatocellular hypertrophy, as well as decreased thyroid colloid area, were observed in both pups and adult animals. The liver and thyroid findings were observed in adult animals at a dose level that was 3-times lower than that producing the same effects in pups. Although thyroid hormone measurements were not taken in this study, there was no evidence of a hyperplastic response in the thyroid. In addition to the effects on liver and thyroid, pup body weights were decreased. The fact that reduced body

weight effects were observed in pups gavage-dosed with buprofezin, as well as pups that were not gavage-dosed but continued to nurse, indicated that buprofezin was transferred via the milk.

The protocol for the definitive developmental thyroid toxicity study was similar to that of the range-finding study, but included an additional group of dams that were gavage-dosed from GD 6-20 for a developmental toxicity assessment. Results of the definitive study demonstrated increases in TSH and liver and thyroid weights as well as histopathology findings in these organs in adult animals and offspring. Findings in dams were similar to those in non-pregnant adult females. At the lowest dose tested, decreased pup body weight/body weight gain in both sexes and increased TSH levels in male pups were observed, and there was also an equivocal increase in fetal thyroid weights. There were no adverse findings in maternal animals at this dose level, thus suggesting sensitivity of the young animal. There was a low level of concern for the findings in the young at the lowest dose level, however, since the body weight effects were transient in nature and the increases in TSH were relatively minor, likely approaching the threshold (NOAEL) for this endpoint.

In the rat 13-week dietary neurotoxicity study, there were no gross or histopathological changes in the central and peripheral nervous system. Reductions in body weight and food consumption were the only findings associated with treatment. On the basis of the findings in this study, as well as consideration of the overall database, the waiver for the acute neurotoxicity study was accepted.

In a mouse 28-day dietary antibody plaque-forming cell immunotoxicity study, buprofezin treatment resulted in decreased spleen weight as well as suppression of anti-SRBC IgM response in females at a relatively high dose. In addition, decreases in body weight, body weight gain and food consumption as well as increases in liver weight were noted in both sexes.

Acute oral toxicity studies in rats revealed high toxicity for the rat metabolites BF4, BF25, and the plant metabolite BF26, and low toxicity for the rat metabolite BF11. No increase in bacterial mutation was observed for any of these metabolites. A rat 28-day oral gavage study with BF-26 identified effects that were not dissimilar from, and occurred at comparable doses to, those observed in rats that were administered buprofezin.

Common names of buprofezin metabolites, as well as the results of the toxicology studies conducted on laboratory animals with buprofezin and its associated end-use product are summarized in Appendix I Tables 2, 3 and 4. The toxicology endpoints for use in the human health risk assessment are summarized in Appendix I, Table 5.

Incident Reports

Since 26 April 2007, registrants have been required by law to report incidents to the PMRA, including adverse effects to Canadian health or the environment. Incidents were searched for the active ingredient buprofezin. Buprofezin is a new active ingredient pending registration for use in Canada. No human or domestic animal incidents involving the active ingredient buprofezin have been reported to the PMRA and the applicant did not submit any additional data. In the United States, there was one reported minor incident involving buprofezin.

3.1.1 *Pest Control Products Act* Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, the database contains the standard complement of required studies, including developmental toxicity studies in rats and rabbits and a reproductive toxicity study in rats. In addition, the toxicity database includes developmental thyroid toxicity studies in rats (range-finding and definitive).

With respect to potential prenatal toxicity, there was a decrease in fetal viability as well as an increase in the incidence of skeletal variations in the rat developmental toxicity study. The findings occurred at a dose that was approaching the limit dose and was also toxic to the maternal animals as demonstrated by effects that included decreases in body weights and food consumption as well as increases in fetal loss. There were no adverse effects on fetal development in the rabbit developmental toxicity study; maternal toxicity was manifested through reductions in body weight, food consumption and fecal output at the highest dose tested. In the reproductive toxicity study, there was evidence of sensitivity of the young with reduced body weight gain in the second generation offspring at a dose that did not elicit maternal toxicity. In the rat developmental thyroid toxicity dose range-finding study, reductions in body weights were observed in pups receiving gavage doses of buprofezin as well as those that were not directly dosed, but received the test chemical through the dam's milk. Effects on liver and thyroid (increased weight and hypertrophy) were observed in both adult females and the offspring; however, the effects in the offspring occurred at a dose 3-fold higher than that producing these effects in adults. Although thyroid hormone measurements were not taken in this range-finding study, there was no evidence of a hyperplastic response in the thyroid and the overall results did not suggest that the young animal would be more sensitive to thyroid toxicity than the maternal animal. In the definitive developmental thyroid toxicity study, however, there was evidence of sensitivity of the young animal. Effects on body weight/body weight gain and TSH levels, as well as equivocal increases in thyroid weights were observed in the young at the lowest dose level, one that did not demonstrate toxicity to the dams.

Overall, the database is adequate for determining sensitivity of the young. As noted above, sensitivity of the young was demonstrated in the rat reproductive toxicity study and the rat developmental thyroid toxicity study. The level of concern for offspring effects in the reproduction study was low due to the nature of the effect. The lack of an offspring NOAEL in the definitive developmental thyroid toxicity study was tempered by the transience of the effects on body weight as well as the minor increases in TSH, both of which suggested that the lowest dose was approaching a NOAEL; thus, an additional factor for use of a LOAEL was not required when considering this study in toxicology endpoint selection. In view of the above, the PCPA factor was reduced to 1-fold for scenarios in which the developmental thyroid toxicity study was selected for risk assessment. For all other scenarios, the risk was considered well-characterized and the PCPA factor was reduced to 1-fold. Toxicology endpoints selected for risk assessment provide protection for the effects noted above, including the serious effect in fetuses (decreased viability) that occurred in the presence of maternal toxicity in the rat developmental toxicity study.

3.2 Acute Reference Dose (ARfD)

To estimate acute dietary risk (1 day), two co-critical studies were selected for risk assessment: the 90-day oral toxicity study in dogs and the developmental toxicity study in rabbits. In the dog study, ataxia was noted within the first few days of dosing at 300 mg/kg bw/day and a NOAEL of 50 mg/kg bw/day was established for this finding. In the rabbit developmental toxicity study, reduced body weight was observed in dams within a first few days of dosing at 250 mg/kg bw/day with a NOAEL of 50 mg/kg bw/day for this finding.

Standard uncertainty factors of 10-fold for interspecies extrapolation as well as 10-fold for intraspecies variability were applied in the setting of the ARfD. For the reasons outlined in the *Pest Control Products Act* Hazard Characterization Section, the *Pest Control Products Act* factor was reduced to 1-fold. The composite assessment factor (CAF) is thus 100-fold.

The ARfD is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{50 \text{ mg/kg bw}}{100} = 0.5 \text{ mg/kg bw of buprofezin}$$

The ARfD provides a margin of 400 to the NOAEL for developmental toxicity in the rat and is considered protective of pregnant women and their fetuses.

3.3 Acceptable Daily Intake (ADI)

To estimate risk from repeat dietary exposure, the two-year rat dietary chronic toxicity/oncogenicity study with a NOAEL of 1.0 mg/kg bw/day was selected. At the LOAEL of 8.7 mg/kg bw/day, decreased body weight and body weight gain, as well as increased incidence of thyroid follicular cell hypertrophy and hyperplasia were observed. This study provides the lowest NOAEL in the database.

Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 1-fold. The CAF is therefore 100.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{1.0 \text{ mg/kg bw/day}}{100} = 0.01 \text{ mg/kg bw/day of buprofezin}$$

Cancer Assessment

The unit risk for buprofezin, denoted by q_1^* (representing the upper 95% confidence limit on the slope of the dose-response curve in the low-dose region) was calculated on the basis of data from the mouse chronic toxicity/carcinogenicity study. A q_1^* of 2.3×10^{-3}(mg/kg bw/day)$^{-1}$ was calculated on the basis of the combined incidence of hepatocellular adenomas/carcinomas in female mice.

3.4 Occupational Risk Assessment

3.4.1 Toxicological Endpoints

Occupational exposure to buprofezin is expected to be mainly via the dermal and inhalation routes for mixer, loaders and applicators (M/L/A), and through the dermal route for postapplication re-entry workers. As the product is proposed for use in greenhouses, the duration of exposure for M/L/A is short- to intermediate-term and long-term for postapplication re-entry workers.

Short-, Intermediate-term Dermal

For short- and intermediate-term dermal risk assessment, the LOAEL of 10 mg/kg bw/day from the rat developmental thyroid toxicity study was selected. The LOAEL was based on decreased pup body weight and increased levels of TSH. Although a 24-day dermal toxicity study in rats was available, it was not selected for endpoint selection since the design of the study did not allow for the assessment of the relevant endpoint in the subpopulation of concern (that is, potential thyroid effect in the developing young).

The target margin of exposure (MOE) for these scenarios is 100, which includes standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The selection of the developmental thyroid toxicity study and MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

A dermal absorption study was not submitted. A dermal absorption factor is required to determine the short- to intermediate-term exposure of mixer/loader/applicators and the long-term exposure of re-entry workers.

From the physical and chemical properties of buprofezin it is not possible to conclude whether it is likely or unlikely to have a high dermal absorption. The molecular weight would suggest that it is a good candidate for high dermal absorption but the log K_{ow} and solubility in water would conclude otherwise. It is not possible to compare potential absorption to other similar chemicals as no other chemical in the thiadiazine class is registered with the Agency.

However, based on the oral absorption value ranging from 40 to 50%, it is unlikely that dermal absorption would be higher than oral absorption. As such, the dermal absorption value used for risk assessment will be reduced from the default of 100% to 50%.

Short-, Intermediate-term Inhalation

For short- and intermediate-term inhalation risk assessment, the LOAEL of 10 mg/kg bw/day from the rat developmental thyroid toxicity study was selected. This LOAEL was based on decreased pup body weight and elevations in TSH. Although the 28-day day rat inhalation toxicity study had a higher NOAEL (25 mg/kg bw/day) and assessed the target tissue (thyroid), it was performed on adult animals and therefore did not address the young animal.

The target MOE for these scenarios is 100, which includes standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The selection of the rat

developmental thyroid toxicity study and MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

Long-term Dermal and Inhalation

For long-term dermal and inhalation risk assessment, the NOAEL of 1 mg/kg bw/day from the two-year dietary chronic toxicity/carcinogenicity study in rats was selected. At a dose of 8.7 mg/kg bw/day, effects included increased incidence of follicular cell hypertrophy and hyperplasia of the thyroid in males.

The target MOE for these scenarios is 100, which includes standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The selection of this study and MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

3.4.2 Occupational Exposure and Risk

Mixer/loader/applicator Exposure and Risk Assessment

Individuals have potential for exposure to buprofezin during mixing, loading and application. Dermal and inhalation exposure estimates for workers open mixing and loading the dry flowable formulation and applying the liquid were generated from the Pesticide Handlers Exposure Database (PHED) (version 1.1).

Exposure estimates were derived for mixer/loaders/applicators applying Applaud Insect Growth Regulator to greenhouse vegetables (cucumbers, peppers and tomatoes) and greenhouse ornamentals (excluding cut flowers), using high and low volume handheld and non-handheld sprayers and non-handheld misters/airblasters. Exposure from mixing and loading Applaud Insect Growth Regulator into non-handheld (that is, automated) devices is considered to be less than that of equipment requiring a person to apply the product manually. The exposure estimates are based on workers wearing a long-sleeved shirt, long pants and chemical resistant gloves and shoes plus socks during mixing, loading, application, clean up and repair.

Dermal exposure was estimated by combining the unit exposure values with the amount of product handled per day and the application rate. Inhalation exposure was estimated by combining the unit exposure values with the amount of product handled per day, the application rate, and 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using 80 kg adult body weight.

The endpoint for short- to intermediate-term exposure via the dermal and inhalation routes is derived from the same toxicological study where effects on the thyroid were identified. Therefore, combined exposure estimates from the dermal and inhalation routes were compared to the toxicological endpoint of concern, as described above, in order to obtain the combined target margin of exposure (MOE) of 100; all calculated MOEs exceeded this target (Appendix I, Tables 6 and 7).

For the cancer risk assessment, it is conservatively estimated that an M/L/A will average 30 days of exposure per year over a 40 year career. The lifespan of a Canadian person is averaged at 78

years. The cancer risk for all workers did not pose a human health concern (Appendix I, Table 8).

3.4.2.2 Exposure and Risk Assessment for Workers Entering Treated Areas

There is potential for exposure to workers re-entering greenhouses treated with Applaud Insect Growth Regulator.

Exposure to greenhouse re-entry workers is expected to be long-term in duration and mainly via the dermal route. Buprofezin is not considered to be volatile based on NAFTA (1999) criteria for product used indoors. The vapour pressure of buprofezin, at the range of temperatures typical of a greenhouse scenario is 4.2×10^{-8} kPa at 20°C and 1.7×10^{-7} kPa at 30°C.

Dermal exposure to workers entering treated areas is estimated by coupling dislodgeable foliar residue (DFR) values with activity-specific transfer coefficients. Activity transfer coefficients are based on ARTF data. Chemical-specific DFR data were submitted for greenhouse tomatoes, which was extrapolated to other greenhouse vegetables because of similar leaf type and cultivation practices. This study collected data at one test site in the United States (California), with a use pattern similar to what is being proposed in Canada. One treated plot, divided into 3 subplots, received two foliar applications at 0.426 kg ai/ha applied with a CO_2 backpack sprayer at 5-day retreatment intervals. DFR samples were collected 1 hour prior to the first application and approximately 0 to 2 hours after the first application. For the second application, samples were collected 1 hour prior to application (5 days after the first application), 0 to 2 hours after application and at 1, 3, 7, 10, 14, 21, 28 and 35 days after application. At each collection period, using a Birkestrand leaf punch sampler, 10 samples at 10.1cm^2 each were collected from each treated subplot and control (untreated) plot for a total of 40 samples with a total leaf surface area of 400 cm^2. Residues were corrected for low average field recoveries of 76% and 71% at 0.005 µg/cm^2 and 0.02 µg/cm^2 fortification levels, respectively. The corrected data after the second application were used for the log linear regression analysis. The equation of the line from the analysis had an r^2 value of 0.8747, indicating that the DFR appears to dissipate according to first order kinetics. The half-life is estimated to be $t_{½}$ = 4.13 days. The percent dislodgeable after the second application was 9% and the slope of the line was used to calculate a percent dissipation per day value of 17%.

However, these data could not be used as a surrogate to refine the DFR for greenhouse ornamentals. As such, for greenhouse ornamentals, the default DFR value of 25% of the application rate and dissipation per day value of 0% were used in the exposure assessment.

Exposure estimates were compared to the toxicological endpoint to obtain the margin of exposure (MOE); the dermal target MOE is 100. Restrictions on spray volumes, application rates, retreatment intervals, and restricted entry interval were required to meet the target MOE (Appendix I, Table 9).

To determine the lifetime cancer risk to re-entry workers, it is estimated that exposure will occur 30 days per year over a 40-year career. A time-weighted average (TWA) approach was used to calculate the DFR value (µg/cm^2). The TWA DFR was calculated for the 30 days of exposure after the first application. While exposure is expected to be long-term, calculating exposure based on residues from the first 30 days is not likely to underestimate long-term exposure (180 – 365 days) since residues are expected to be the highest during the first 30 days.

The cancer risk for all workers is not of concern (Appendix I, Table 10).

3.4.2.3 Bystander Exposure and Risk

Bystander exposure should be negligible since the potential for drift is expected to be minimal as application is limited to greenhouse ornamentals (excluding cut flowers), groundcovers, landscape plants and vegetables (peppers, cucumbers and tomatoes).

3.5 Food Residues Exposure Assessment

3.5.1 Residues in Plant

The residue definition for risk assessment and enforcement in plant products is buprofezin. The data gathering/enforcement analytical method is valid for the quantitation of buprofezin residues in crop matrices. The residues of buprofezin are stable in a variety of crops for up to 1429 days when stored in a freezer at -20°C. The residues of buprofezin are stable in representative matrices from five crop categories (high water, high oil, high protein, high starch and high acid content) for up to 370 days when stored at -20°C. Therefore, buprofezin residues are considered stable in all frozen crop matrices and processed crop fractions for up to 370 days. Buprofezin residues concentrated in the following processed commodities: dried plums (2.1×), raisins (2.4×), orange oil (30×), tomato paste (1.3×), and olive oil (3.1×). Crop field trials conducted throughout Canada and the United States using end-use products containing buprofezin at approved (or exaggerated) rates in or on banana, snap beans, strawberries, broccoli, cabbage, mustard greens, coffee, cotton, oranges, apples, pears, peaches, plums, cherries, grapes, head lettuce, leaf lettuce, spinach, lychee, olives, papayas, almonds, pecans, tomatoes, peppers, cucumbers, muskmelons, summer squash, and tea are sufficient to support the proposed maximum residue limits.

3.5.2 Dietary Risk Assessment

Acute and chronic (cancer and non-cancer) dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™).

3.5.2.1 Chronic Dietary Exposure Results and Characterization

The following criteria were applied to the refined chronic non-cancer analysis for buprofezin: 100% crop treated, default and experimental processing factors (where available), residues on some crops based on supervised trial median residue (STMdR) values, and monitoring data for other crops. The refined chronic dietary exposure from all supported buprofezin food uses (alone) for the total population, including infants and children, and all representative population subgroups is less than 8% of the acceptable daily intake (ADI). Aggregate exposure from food and drinking water was not conducted since there is no expectation of buprofezin in drinking water as the current use is for greenhouses.

The refined chronic cancer risk assessment was conducted with the same criteria used for the chronic non-cancer assessment. The lifetime cancer risk from exposure to buprofezin in food was estimated to be 7×10^{-7} for the general population, which is not of health concern.

3.5.2.2 Acute Dietary Exposure Results and Characterization

The following assumptions were applied in the basic acute analysis for buprofezin: 100% crop treated, default processing factors, and residues in/on crops at MRL levels. The refined acute dietary exposure (food alone) for all supported buprofezin registered commodities is estimated to be <48% (0.24 mg/kg bw/day) of the ARfD for all population subgroups (95th percentile, deterministic).

3.5.3 Aggregate Exposure and Risk

The aggregate risk for buprofezin consists of exposure from food only; there are no residential uses. There is no expectation of buprofezin in drinking water from greenhouse use and importation of food crops from the US which may have been treated with buprofezin.

3.5.4 Maximum Residue Limits

The recommendation for maximum residue limits (MRLs) for buprofezin was based upon the submitted field trial data, and the guidance provided in the OECD MRL Calculator. MRLs to cover residues of buprofezin in/on crops and processed commodities are proposed as shown in Table 3.5.1. Residues in processed commodities not listed in Table 3.5.1 are covered under the proposed MRLs for the raw agricultural commodities (RACs).

Table 3.5.4.1 Proposed Maximum Residue Limits

Commodity	Recommended MRL (ppm)
Citrus oil	80
Leafy *Brassica* greens (CSG 5B)	60
Leafy Vegetables (Except *Brassica* Vegetables) (CG 4)	35
Tea	30
Head and Stem *Brassica* (CSG 5A)	12
Peach subgroup (CSG 12-09B)	9
Pears, Asian pears	6
Olives	5
Orange subgroup (CSG 10 A)	4
Low growing berry (CSG 13-07G), apples, crabapples, loquats, mayhaws, quinces	3
Fruiting Vegetables (CG 8-09), Cherry subgroup (CSG 12-09A), Plum subgroup (CSG 12-09C), raisins	2
Grapes	1
Papayas, star apples, black sapotes, mangos, sapodillas, canistels, mamey sapotes	0.9
Cucurbit Vegetables (CG 9)	0.7

Commodity	Recommended MRL (ppm)
Lychees, avocados, bananas, sugar apples, cherimoyas, atemoyas, custard apples, illamas, soursops, bieltas, longans, Spanish limes, rambutans, pulasans, guavas, feijoas, jaboticabas, wax jambus, starfruits, passionfruits, acerolas	0.3
Green coffee beans, undelinted cotton seeds	0.25
Tree Nuts (CG 14-11)	0.05
Edible-podded snap beans	0.02

MRLs are proposed for each commodity included in the listed crop groupings in accordance with the Residue Chemistry Crop Groups webpage in the Pesticides and Pest Management section of Health Canada's website.

For additional information on maximum residue limits (MRLs) in terms of the international situation and trade implications, refer to Appendix II.

The nature of the residues in plant matrices, analytical methodologies, field trial data, and acute and chronic (cancer and non-cancer) dietary risk estimates are summarized in Appendix I, Tables 11, 12 and 13.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Environmental Fate

Buprofezin is not expected to volatilise from moist soil and water surfaces (Henry's Law Constant = 6.71×10^{-7} atm m^3/mole at 25°C). Photostransformation is not a route of transformation of buprofezin in soil or water. Buprofezin is classified as slightly mobile in soil (K_{oc} = 2100 – 4800) and was not mobile in an aged soil leaching study (85-100% remained in top 8 cm of soil). The primary routes of dissipation in the environment are microbially-mediated biotransformation in aerobic soils with a half-life in aerobic soils of 26-70 days. The biotransformation of buprofezin in soils does not result in any major transformation products. Buprofezin does not undergo photolytic reactions on soil surfaces. Buprofezin is considered to have low to slight potential for leaching based upon the results of laboratory studies.

Buprofezin is slightly persistent in aerobic aquatic systems (DT_{50} = 47-51 days), is sparingly soluble in water, and as such is expected to partition to sediments in aquatic environments. Photostransformation is not expected to be a major route of transformation as buprofezin has a photolysis half-life of 38 days. In aquatic systems, buprofezin will likely partition to sediment or suspended particles due to its high soil/water partitioning coefficients. Buprofezin was shown to be stable to hydrolysis at pH 7 and 9 for up to 30 days. At pH 5, buprofezin degraded with a calculated half-life of 51 days to two major transformation products, BF12 (1-isopropyl-3-phenylurea) and BF25 (N-[[(1,1-dimethylethyl)amino]thioxomethyl]-N-(1-methylethyl)-N-phenylurea). This is consistent with the UV/vis absorption spectrum which showed a significant shift of the UV/vis maximum absorbance, indicating protonation in acidic solutions. In anaerobic

aquatic environments, buprofezin is considered to be stable to microbial biotransformation with a transformation half-life of 1,200 days with no major transformation products identified.

Buprofezin has a log K_{ow} = 4.31 which indicates a potential for bioaccumulation and triggers a need for a bioconcentration study. A bioaccumulation test using bluegill sunfish showed buprofezin had a bioconcentration factor of 678–98 with rapid depuration half-life of 0.5 days on cessation of exposure. As depuration of buprofezin from fish tissues was rapid this behaviour is expected to limit the bioconcentration of buprofezin in fish.

4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated environmental exposure concentrations (EEC's) are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EEC's are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (in other words, protection at the community-, population-, or individual level).

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the risk quotient is then compared to the level of concern (LOC = 1). If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary. If the screening level risk quotient is equal to or greater than the level of concern, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

4.2.1 Risks to Terrestrial Organisms

Three studies for honey bees were submitted and reviewed (contact, oral toxicity tests and a Tier I brood study). All three studies were classified as reliable. Four studies for beneficial terrestrial arthropods were submitted and reviewed. Three studies were laboratory studies and one was a field study. The field study was conducted in a grape orchard in Switzerland and was deemed unreliable. One of the laboratory studies, a contact toxicity test conducted with the

predatory mite *Phytoseiulus persimilis*, was found to be unreliable due to a flawed study design. The remaining two laboratory studies submitted were found to be reliable with restrictions.

Effects on Honey bees

Data for acute oral and contact toxicity of buprofezin to honey bees was submitted in addition to a honey bee hive study that included brood. Buprofezin is considered relatively non-toxic to bees with respect to acute contact and acute oral toxicity.

The oral toxicity of buprofezin to the honey bee (*Apis mellifera L.*) was determined in a limit test to be >933.58 ug a.i./bee. No abnormal behaviour was noted in either the buprofezin treatment group, relative to the control. No mortality was observed in the buprofezin treatment group after 48 hours. On a contact exposure basis, a contact LD_{50} >200 ug a.i./bee classifies buprofezin as relatively non-toxic to honey bees. The risk to bees was determined to be negligible (RQ = 0.003–0.026) and thus did not exceed the LOC.

A Tier 1 brood study was conducted to study the effects of buprofezin on honey bee brood (*Apis mellifera L.*). This test is a qualitative test method (OECD 237/*DRAFT*2007)22 and is considered as a screening level test. The results indicate that when adult worker bees are dosed with 2.67 g Buprofezin 25WP/hive (0.67 g buprofezin/hive), no deleterious effects to brood were observed. It should be noted that the dose used in this test cannot be translated to the proposed maximum application rate of buprofezin for greenhouse ornamentals and landscape plants of 686 g a.i./ha. There is insufficient data available, particularly on exposure of brood, to relate larval toxicity to field application rates and brood damage. Due to the use pattern in greenhouses only, a semi-field or field test is not required but may be required in future if the use pattern changes.

Beneficial Terrestrial Arthropods

A 14-day acute contact/reproductive toxicity study on predatory mites (*Typhlodromus pyri*) showed a 7-day LR_{50} >937.5 mg a.i./kg and the 14-day ER_{50} >937.5 mg a.i./kg based on reduction in reproduction, both equivalent to an EP application rate of 100 kg ai/ha. Although the application rate of the test substance in this test exceeded the maximum proposed application rate for greenhouse in Canada by about 100 times, no statistically significant effects on mortality or reproduction are expected for the proposed maximum application rate for Applaud Insect Growth Regulator of 0.686 kg a.i./ha.

An additional test on *Encarsia formosa* adults and protected stage (pupae) showed a 24-hour acute contact LR_{50} >82.5 kg a.i./ha and a 14-day ER_{50} >82.5 kg a.i./ha based on reduction in reproduction. There was no reduction in the parasitization rate relative to the control at the tested treatment rates. No mortality was observed after 24 hours in either the control or test substance groups. It should be noted that the maximum proposed application rate of Applaud Insect Growth Regulator for greenhouses is 686 g a.i./ha (0.686 kg a.i./ha) or about 80 times lower than used in the test. See Appendix II, Table 14 for endpoints.

4.2.2 Risks to Aquatic Organisms

Buprofezin was classified as highly toxic to aquatic invertebrates based upon the endpoint from the 48-hour acute study conducted on *Daphnia sp.* where the 48-hour LC_{50} was equal to 0.84 mg a.i./L. Definitive endpoints for fish, both cold and warm water species could not be derived as the LC_{50}s for both cold and warm water fish were reported as >0.33 mg a.i./L. As such it cannot be ruled out that buprofezin may be highly toxic to aquatic organisms. Reproductive effects to aquatic invertebrates were noted at 0.12 mg a.i./L in a 21 day chronic study conducted on *Daphnia sp.* See Appendix I, Table 15.

Although buprofezin could pose a risk to aquatic organisms if contaminated greenhouse effluent is released in quantities that are toxic to invertebrates and fish, the greenhouse only use pattern and mitigation statement proposed for the label mean it is not expected to pose an unacceptable risk.

5.0 Value

5.1 Consideration of Benefits

Applaud Insect Growth Regulator has value because it controls whiteflies when sprayed on the foliage of greenhouse cucumbers, peppers, tomatoes and greenhouse ornamentals (excluding cut flowers). Whiteflies are major pests in greenhouses and have developed resistance to most of the registered conventional insecticides. Because the mode of action of buprofezin is new to Canada, it will contribute to resistance management of insecticide resistance of whiteflies in greenhouses. However, there are isolated cases of whitefly resistance to buprofezin in Europe, Israel, Pakistan and the United States, which indicates the need for careful stewardship.

Alternative active ingredients registered for use against whiteflies on greenhouse cucumber, pepper and tomato include conventional ones such as insect growth regulators, neonicotinoids, pyrethroids and organophosphates. Registered alternatives also include nonconventional active ingredients such as insecticidal soap, insect pathogens and mineral oil. The alternatives for use against whiteflies on greenhouse ornamentals include those listed for greenhouse vegetables plus diamides and feeding blockers. There have been reports of resistance to all listed conventional alternatives except for the diamides.

The uses of Applaud Insect Growth Regulator on greenhouse cucumber, pepper, tomato, and ornamentals to control whiteflies were identified as high priorities in the Canadian Grower Priority Database. Additionally, the product may be used as part of greenhouse integrated pest management programs and is also compatible with other greenhouse management strategies.

5.2 Effectiveness Against Pests

Eighteen efficacy trials were provided to support label claims for whiteflies on labelled crops. Fifteen greenhouse trials on vegetable crops were conducted in Europe and three greenhouse trials on ornamentals were conducted in the US. Conditions in these trials were similar to those in Canadian greenhouses. The trials demonstrated that the product was effective against whitefly larvae and that it suppressed egg production and reduced egg viability.

5.3 Non-Safety Adverse Effects

There were no reports of adverse effects in any of the submitted trials.

5.4 Supported Uses

Applaud Insect Growth Regulator controls whiteflies at 36-43 g product/100 L on greenhouse cucumber, pepper, tomato and ornamentals (excluding cut flowers).

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy: persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*.

During the review process, buprofezin was assessed in accordance with the PMRA Regulatory Directive DIR99-03[5] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Buprofezin does not meet all Track 1 criteria, and is not considered a Track 1 substance. See Table 6.2.1 for comparison with Track 1 criteria.
- Buprofezin does not form any transformation products that meet all Track 1 criteria.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*.[6]

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5 DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*.

6 *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette*, Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

The list is used as described in the PMRA Notice of Intent NOI2005-01[7] and is based on existing policies and regulations including DIR99-03 and DIR2006-02,[8] and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Technical grade buprofezin does not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette*.
- The end-use product, Applaud Insect Growth Regulator, contains formulants which are identified in the *Canada Gazette* as formulants of health or environmental concern that are allergens known to cause anaphylactic-type reactions. Therefore, the label for the end-use product Applaud Insect Growth Regulator will include the precautionary statement: "Warning: this product contains the allergens sulfites on the principal display panel.
- The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02.

Toxic Substance Management Policy Considerations

Table 6.2.1 Toxic Substances Management Policy Considerations – Comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Active Ingredient Endpoints
Toxic or toxic equivalent as defined by the *Canadian Environmental Protection Act*[1]	Yes		Yes
Predominantly anthropogenic[2]	Yes		Yes
Persistence[3]:	Soil	Half-life ≥ 182 days	Half-life = 70 days
	Water	Half-life ≥ 182 days	Half-life = 51 days
	Sediment	Half-life ≥ 365 days	Half-life >365 days
	Air	Half-life ≥ 2 days or evidence of long range transport	Half-life or volatilisation is not expected to be a route of dissipation based on the vapour pressure (8.5×10^{-5} Pa at 25 °C) and Henry's Law Constant (6.71×10^{-7} atm m^3 / mole) and long-range atmospheric transport is unlikely to occur as the half-life in air is 2.4 hours.
Bioaccumulation[4]	Log $K_{OW} \geq 5$		4.31 (at pH 7)
	BCF ≥ 5000		464
	BAF ≥ 5000		not available
Is the chemical a TSMP Track 1 substance (all four			No, does not meet TSMP Track 1 criteria.

7 NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act*.

8 DIR2006-02, *Formulants Policy and Implementation Guidance Document*.

TSMP Track 1 Criteria	TSMP Track 1 Criterion value	Active Ingredient Endpoints
criteria must be met)?		

[1] All pesticides will be considered toxic or toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the toxicity criterion may be refined if required (in other words, all other TSMP criteria are met).
[2] The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.
[3] If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.
[4] Field data (for example, BAFs) are preferred over laboratory data (for example, BCFs) which, in turn, are preferred over chemical properties (for example, log K_{OW}).

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for buprofezin is adequate to define the majority of toxic effects that may result from exposure. In short-term and chronic studies on laboratory animals, the primary targets of toxicity were the liver and the thyroid. Buprofezin was not considered genotoxic but there was some evidence of aneugenic activity. Liver tumors were observed in mice but not rats following chronic exposure. Buprofezin was not neurotoxic. There was evidence of dysregulation of the immune system in rats. Buprofezin did not cause any adverse effects on reproduction in parental rats; however decreased body weight gain in offspring at a dose that was not toxic to parental animals indicated sensitivity of the young. In the rat developmental toxicity study, fetal death was observed at a dose that also produced toxicity in maternal animals. Although the young animal appeared to be more sensitive than the adult animal to thyroid toxicity, overall, the nature and strength of the thyroid findings in the young animal suggested a low level of concern. The risk assessment protects against the toxic effects noted above by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Mixer, loader, applicators handling Applaud Insect Growth Regulator and workers re-entering treated areas within greenhouses are not expected to be exposed to levels of buprofezin that will result in unacceptable risks when the Applaud Insect Growth Regulator is used according to label directions. Label amendments on personal protective equipment and limitations on the application equipment, application rate, plants, spray volume, retreatment interval and restricted entry interval are adequate to protect mixer, loader, applicators and re-entry workers.

The nature of the residues in plants is adequately understood. The residue definition for risk assessment and enforcement is buprofezin in plant products. The proposed use of buprofezin on greenhouse cucumbers, tomatoes, and peppers does not constitute a health risk of concern for chronic (cancer and non-cancer) or acute dietary exposure (food only) to any segment of the population, including infants, children, adults and seniors. Sufficient crop residue data have been reviewed to recommend MRLs. The PMRA recommends that the following MRLs be specified for residues buprofezin:

Commodity	Recommended MRL (ppm)
Citrus oil	80
Leafy *Brassica* greens (CSG 5B)	60

Leafy Vegetables (Except *Brassica* Vegetables) (CG 4)	35
Tea	30
Head and Stem *Brassica* (CSG 5A)	12
Peach subgroup (CSG 12-09B)	9
Pears, Asian pears	6
Olives	5
Orange subgroup (CSG 10 A)	4
Low growing berry (CSG 13-07G), apples, crabapples, loquats, mayhaws, quinces	3
Fruiting Vegetables (CG 8-09), Cherry subgroup (CSG 12-09A), Plum subgroup (CSG 12-09C), raisins	2
Grapes	1
Papayas, star apples, black sapotes, mangos, sapodillas, canistels, mamey sapotes	0.9
Cucurbit Vegetables (CG 9)	0.7
Lychees, avocados, bananas, sugar apples, cherimoyas, atemoyas, custard apples, ilamas, soursops, birbas, longans, Spanish limes, rambutans, pulasans, guavas, feijoas, jaboticabas, wax jambus, starfruits, passionfruits, acerolas	0.3
Green coffee beans, undelinted cotton seeds	0.35
Tree Nuts (CG 14-11)	0.05
Edible-podded snap beans	0.02

7.2 Environmental Risk

Buprofezin has potential to volatilise from moist soil and water surfaces based on Henry's Law Constant. Buprofezin is slightly to moderately persistent in aerobic soils. The primary routes of dissipation in the environment are microbially-mediated degradation in aerobic soils and adsorption to soil particles. Buprofezin is considered to have low to slight potential for leaching based upon the results of laboratory studies although buprofezin may leach in sand/sandy clay loam soils.

In water, buprofezin is considered slightly persistent. Buprofezin is considered sparingly soluble in water and as such, is not expected to partition to water. In water, buprofezin will likely remain bound to sediment or suspended particles due to its high soil/water partitioning coefficients. In anaerobic aquatic environments, buprofezin is considered to be stable to microbial biotransformation. There is potential for buprofezin to bioaccumulate in fish although data reviewed shows depuration of buprofezin from fish tissues to be rapid. This behaviour is expected to limit the bioconcentraion of buprofezin in fish.

Buprofezin is considered relatively non-toxic to bees on an acute oral and contact toxicity basis. Results from the bee brood study indicated that no deleterious effects are expected to brood. The risk from buprofezin use in greenhouses on tomatoes, cucumbers and peppers to bees and beneficial arthropods is considered to be negligible.

In the aquatic environment, buprofezin has the potential to pose a risk to aquatic organisms *if* greenhouse effluent enters surface water via effluent run-off from greenhouses and soil run-off

into aquatic environments. However, the mitigation statement on the product label should prevent this.

Buprofezin was classified as highly toxic to aquatic invertebrates based on an acute toxicity study conducted on *Daphnia sp.* Definitive endpoints for fish, both cold and warm water species could not be derived. As such it cannot be ruled out that buprofezin may be highly toxic to aquatic organisms. Exposure to aquatic organisms cannot be estimated although toxicity endpoints for aquatic organisms have been reviewed. Despite this, mitigation statements to minimize risk to aquatic organisms are required for all greenhouse uses, regardless of toxicity to aquatic organisms and will be added to the proposed label for Applaud Insect Growth Regulator.

7.3 Value

Sufficient value information was supplied to support the use of Applaud Insect Growth Regulator to control whiteflies on greenhouse cucumber, pepper, tomato and greenhouse ornamentals (excluding cut flowers). Whiteflies are a major pest in greenhouses and have developed resistance to most of the currently registered conventional insecticides. Because the mode of action of buprofezin, the active ingredient in Applaud Insect Growth Regulator, is new to Canada, it will aid in the management of insecticide resistance of whiteflies in greenhouses. Growers have identified this product as a high priority for control of whiteflies on greenhouse cucumber, pepper, tomato, and ornamentals. Additionally, the product may be used as part of greenhouse integrated pest management programs and is also compatible with other greenhouse management strategies.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Buprofezin Technical and Applaud Insect Growth Regulator, containing the technical grade active ingredient buprofezin, to control whiteflies on greenhouse vegetables (cucumbers, peppers and tomatoes) and greenhouse ornamentals (excluding cut flowers).

Furthermore, establishment of MRLs for residues of buprofezin in/on food crops that may be imported into Canada is proposed.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

List of Abbreviations

♀	female
♂	male
µg	micrograms
4NP-UDP-GT	4-nitrophenol-uridine diphosphate-glucuronosyltransferase
abs	absolute
AD	administered dose
ADD	average daily dose
ADME	absorption distribution metabolism excretion
ADI	acceptable daily intake
a.i.	active ingredient
ALK	alkaline phosphatse
ALT	alanine aminotransferase
Anti-SRBC	anti-sheep red blood cell
APTT	activated partial thromboplastin time
ARfD	acute reference dose
ARI	aggregate risk index
AST	serum aspartate amino-transferase
atm	atmosphere
ATPD	area treated per day
BAF	bioaccumulation factor
BCF	bioconcentration factor
bw	body weight
bwg	bodyweight gain
°C	degrees Centigrade
CAF	composite assessment factor
CAS	chemical abstracts service
cm	centimetres
Cmax	maximum serum concentration
CYP2B	cytochrome P450 2B isozyme
DEEM-FCID	dietary exposure evaluation model
DF	dry flowable
DFR	dislodgeable foliar residue
DNA	deoxyribonucleic acid
DT_{50}	dissipation time 50% (the time required to observe a 50% decline in concentration)
DT_{90}	dissipation time 90% (the time required to observe a 90% decline in concentration)
E.coli	*Escherichia coli*
EC_{50}	effective concentration on 50% of the population
EEC	estimated environmental exposure concentration
ER_{50}	effective rate on 50% of the population
EFSA	European Food Safety Authority
F_2	second generation
fc	food consumption
FDA	*Food and Drugs Act*

fe	food efficiency
g	gram(s)
GC-NPD	gas chromatography – nitrogen / phosphorus detection
GC-MS	gas chromatography mass spectroscopy
GD	gestation day
GIT	gastro intestinal tract
GLP	good laboratory practices
h	hour
ha	hectare(s)
HAFT	highest average field trial
HDPE	high density polyethylene
HDT	highest dose tested
HPLC-UV	high performance liquid chromatography – ultraviolet detection
IUPAC	International Union of Pure and Applied Chemistry
K	Henry's Law Constant
kg	kilogram(s)
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*–octanol-water partition coefficient
kPa	kiloPascal
L	litre(s)
LADD	lifetime average daily dose
LC_{50}	lethal concentration to 50%
LD	lactation day
LD_{50}	lethal dose to 50%
LOAEL	lowest observed adverse effect level
LOEC	lowest observed effect concentration
LOC	level of concern
LOQ	limit of quantitation
LR_{50}	lethal rate 50%
M/L/A	mixer/loader/applicator
mg	milligram(s)
mm	millimetre(s)
MAS	maximum average score for 24, 48 and 72 hours
MIS	maximum irritation score
MOA	mode of action
MOE	margin of exposure
MRL	maximum residue limit
MS	mass spectrometry
N/A	not applicable
NAFTA	North American Free Trade Agreement
nm	nanometre
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
N/R	not required
NZW	New Zealand white
OECD	Organization for Economic Cooperation and Development
OM	organic matter content

pKa	dissociation constant
Pa	Pascals
PBI	protein-bound iodine
PCPA	*Pest Control Products Act*
PFC/Spleen	plaque-forming cells from the spleen
PHED	Pesticide Handlers Exposure Database
PHI	preharvest interval
PMRA	Pest Management Regulatory Agency
PND	postnatal day
PPE	personal protection equipment
ppm	parts per million
PROD	pentoxyresorufin-*O*-dealkylase
PTU	propylthiouracil
q_1^*	Q-star cancer potency factor
r^2	Coefficient of determination
RAC	raw agricultural commodity
RI	Risk Index
rel	relative
RQ	risk quotient
SC	suspension concentrate
SD	standard deviation
SRBC	sheep red blood cell
STMdR	supervised trial median residue
T3	tri-iodothyronine
T4	thyroxine
TC	Transfer coefficient
TGAI	technical grade active ingredient
Tmax	the time at which maximum serum concentration is achieved
TPO	thyroid peroxidase
TRR	total radioactive residue
TSH	thyroid stimulating hormone
TSMP	Toxic Substances Management Policy
TWA	Time – weighted average
UDP-GT	uridine diphosphate glucuronyltransferase
US	United States
USEPA	United States Environmental Protection Agency
UV	ultraviolet
wc	water consumption
wt	weight

Appendix I Tables and Figures

Table 1 Residue Analysis

Matrix	Method ID	Analyte	Method Type	LOQ	Reference
Soil / Sediment	BF/04/94	active	GC-NPD	0.01 ppm	PMRA # 2179640
		BF-12 metabolite		0.01 ppm	
Water	GE-04, 05-0338	active	HPLC-UV	0.1 µg/L	PMRA # 2314207

Table 2 Names of Select Buprofezin Metabolites

Compound / Metabolite	Chemical Name
A4	4-hydroxyaniline
A5	p-acetaminophenol
A6	N-4-hydroxyphenyl-N'-isopropylurea
A7	2-tert-butylimino-3-isopropyl-5-(4-hydroxy-phenyl) perhydro-1,3,5-thiadiazin-4-one
A12	2-tert-butylimino-3-isopropyl-5-phenyl-perhydro-1,3,5-thiadiazin-4-one-1-oxide
A13	2-tert-butylamino-5-phenyl-5,6-dihydro-4H-1,3,5-thiadiazin-4-one
A15	2-tert-butylimino-5-(3,4-dimethoxyphenyl)-3-isopropyl-3,4,5,6-tetrahydro-2H-1,3,5-thiadiazin-4-one
BF 2	4-hydroxybuprofezin
BF 4	tert-butylhydroxy-buprofezin
BF 9	2-tert-butylimino-3-isopropyl-5-phenyl-1,3,5-thiadiazinan-2,4-dione
BF 10	2-tert-butylimino-3-isopropyl-5-phenyl-1,3,5-thiadiazinan-4-one-1-oxide (also known as buprofezin sulfoxide)
BF 11	phenylbiuret
BF 12	1-isopropyl-3-phenylurea (also known as isopropylphenylurea)
BF 13	1-(4-hydroxyphenyl)-3-isopropylurea (also known as 2-hydroxyisopropylphenyl-urea)
BF 22	4-aminophenol
BF 23	N-(4-hydroxyphenyl)acetamide
BF 25	diethiuret
BF 26	2-amino-2-methylpropylphenylcarbamoyl propan-2-ylcarbamate
BF 27	2-tert-butylimino-5-(4-hydroxy-3-methoxyphenyl)-3-isopropyl-1,3,5-thiazinan-4-one) (also known as hydroxyl-methoxy-buprofezin)
BF 28	2-[3-isopropyl-3-(methylsulfonylmethylphenylcarbamoyl)ureido-2-methylpropionic acid
C	dihydroxy-buprofezin

Table 3 Toxicity Profile of End-use Products Containing Buprofezin

Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons.

Study Type/ Animal/ PMRA #	Study Results
End Use Product – Applaud Insect Growth Regulator	
Acute oral toxicity Rat (Wistar) PMRA #2170897	LD_{50} > 5000 mg/kg bw Low toxicity
Acute dermal toxicity Rat (Sprague-Dawley) PMRA #2170901	LD_{50} > 2000 mg/kg bw Low toxicity
Acute inhalation toxicity (nose-only) Rat (Wistar) PMRA #2170898	LC_{50} > 2.2 mg/L Low toxicity
Dermal irritation Rabbit (NZW) PMRA #2170899	MEAN = 1, MIN = 3 (1h) Slightly irritating
Eye irritation Rabbit (NZW) PMRA #2170902	MEAN = 3.7 MIN = 14.3 (1h) Mildly irritating (due to persistence at 72 hours)
Dermal sensitization (Buehler test) Guinea pig (Hartley) PMRA #2170925	Non-sensitizer

Table 6 Toxicity Profile of Technical Bispyribac

Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to body weights unless otherwise noted. Effects seen above the LOAEL(s) have not been reported in this table for most studies for reasons of brevity.

Study Type/ Animal/ PMRA #	Study Results
ADME following single oral dose (low and high) Rat (Sprague-Dawley) PMRA # 2170620	Absorption: T_{max} of 3 hours; C_{max} was proportional to dose. Excretion: Elimination from blood was biphasic with half-lives of 13 and 60 hours. For the low dose, 82% of the AD was excreted within 24 hours and 93% of the administered dose (AD) was excreted with 48 hours. For the high dose, the excretion was slightly delayed, but 91% of the AD was still eliminated within 48 hours. Overall, 70-74% of the AD was excreted in the feces and 21-25% of the AD was excreted in the urine. In bile duct cannulated rats (low dose only), 35% of the AD was excreted in the bile. Minimal radioactivity (< 0.9% of AD) was detected in expired air. Distribution: Within 2 hours post-dosing, bispyribac was widely distributed into tissues, with highest concentrations in adipose tissue, kidney, liver and urinary bladder at most of the time points between 2 and 96 hours. At the low dose, elimination from the thyroid was slower than from other organs. At the high dose, radioactivity concentrations in many organs were higher than proportional to the AD at several time points but not at study termination (96 hours). Metabolism: Parent compound was identified in feces (12% of the AD). Metabolism occurred via hydroxylation with methylation of the phenyl ring, oxidation of sulfur with consecutive opening of the thiadiazinone ring and conjugation reactions with sulfate and glucuronic acid. Identified metabolites included BF 01, BF 02, BF 21, C, and BF 27, as well as BF 03 (in vitro only). Further characterization of metabolites led to the identification of glucuronic acid and/or sulfuric acid conjugates of BF 22 and BF 23.

Study Type/Animal/PMRA #	Study Results
Excretion, distribution and metabolism following *single oral dose* (low and high) Rat (Sprague Dawley) PMRA 2179635	Excretion: In males, 90-91% of the AD was excreted by 48 hours post-dose (20-22% in urine; 69-71% in feces). In females, 87-89% of the AD was excreted by 48 hours post-dose (13-15% in urine; 73-76% in feces). Elimination was faster in males than in females in the first 24 hours but was fairly even by 48 hours post-dose. Minimal radioactivity (<0.5% of AD) was detected in expired air. In bile duct-cannulated rats, 30% of the AD in males and 36% of the AD in females was recovered in bile at 24 hours post-dose. Only 3-5% of the AD was found in the urine. These results suggest the enterohepatic recirculation of *buprofezin*. Distribution: At 7 days post-dose, <1% of the AD remained in the body. At both doses in males and females, the highest concentrations of radioactivity were found in blood cells, the thyroid and the liver. The radioactivity in the GIT of females was higher than in males, suggesting that absorption in females might be slower than in males. Metabolism: Components identified in feces included parent compound (at least 10% of the AD at the low dose and 8% of the AD at the high dose), A7/BF2 (at least 0.4% at the low dose and 1.8% at the high dose), and A15/BF20 (not quantified). Radioactivity remained primarily in the aqueous layer, indicating the presence of polar metabolites. In bile duct-cannulated rats, parent compound was identified in feces. No other components were identified, suggesting that fecal metabolites were derived from bile, although they were not detected in the analysis of bile, possibly due to conjugation.

Study Type/Animal/PMRA #	Study Results
Metabolism following single oral dose (high) PMRA 2179636	Metabolism: In urine, conjugated and free forms of components were identified, including A5, A6, A7, A13, phenylurea, and possibly A4. Glucuronide and sulfate conjugates in urine made up 9.8% and 2.7% of the AD, respectively, and together represented 67% of the total radioactivity in urine. In feces from rats that were not cannulated, parent compound (4% of the AD), A7 (0.7% AD) and possibly A12 (0.7% AD) were identified. Minor components (in total making up 5% of the AD) included A5, A6, A13 and phenylurea. Glucuronide conjugates made up 15% and 6% of the AD in males and females, respectively. In bile, A5, A6, A13 and phenylurea were identified. Glucuronide and sulfate conjugates in bile made up 12% and 0.1% of the AD, respectively, and together represented 43% of the total radioactivity in bile. In feces from bile duct-cannulated rats, only parent compound was identified. This suggested that the other components in feces from rats that were not cannulated were derived from bile, although they were not detected in the analysis of bile, possibly due to conjugation. Enzyme-mediated deconjugation of urine, feces and bile extracts greatly increased the quantity of labile radioactivity, particularly after β-glucuronidase treatment. The results demonstrated extensive metabolism of buprofezin via hydroxylation of the phenyl ring moiety, removal of the isopropyl group, and oxidation of sulfur leading to eventual cleavage with the thiadiazin ring. Glucuronide and sulfate conjugation of metabolites, but not of buprofezin, explains the highly polar nature of the radioactivity in urine, feces and bile.

Study Type/Animal/PMRA #	Study Results
Excretion, distribution and metabolism following single oral dose (high) Rat (Sprague Dawley) PMRA 2179634	Excretion: 82% of AD was excreted within 24 hours and 95% of AD was excreted within 72 hours. At 72 hours, fecal elimination accounted for 79% of the AD and urinary excretion accounted for 13% of the AD. Distribution: At 72 hours, tissues contained 0.4% of the AD; residual carcass contained 0.4% of the AD. The highest levels of radioactivity were found in the kidney, blood, thyroid and liver. Metabolism: Extractable metabolites in feces included unchanged parent (45% of AD), BF27 (7% of AD) and BF28 (5% of AD). Other trace metabolites (BF9, BF10, BF12, BF13) were identified after hydrolysis of the unextractable fecal residue. Urine contained polar conjugates which upon hydrolysis with sulfatase released BF13 (0.5% of AD), BF23 (2.5% of AD) and BF28 (0.3% of AD). Significant improvement in identification of the residue was achieved over previous studies, with more than 60% of the AD being identified. No single unknown or unextractable residue exceeded 3.7% of the AD. The metabolic pathway involves phenyl ring hydroxylation, oxidation of the t-butyl group and thiadiazinane ring opening with extensive conjugation of metabolites.
Supplemental metabolism study to identify early metabolites in organs after single oral dose (high) Rat (Sprague Dawley) PMRA 2485744	Apart from previously identified metabolites, the liver homogenates were found to contain BF4, BF11, and BF25.
Accumulation in rats following repeated oral doses (24 week dietary study) Rat (Sprague Dawley) PMRA 2179635 PMRA 2485744	200 ppm: After 24 weeks of dosing, buprofezin was detected at 0.58 to 0.86 ppm in adipose tissue, < 0.1 to 0.16 ppm in liver, and < 0.1 ppm in other tissues. 1000 ppm: After 24 weeks of dosing, buprofezin was detected at 3.4 ppm in adipose tissue, 0.15 to 0.34 ppm in liver, and < 0.1 ppm in other tissues. The results indicated that buprofezin did not accumulate in rat tissues after oral administration. However, the analysis was limited to buprofezin and no conclusion about the metabolite profiles in tissues could be drawn.

Study Type/Animal/PMRA #	Study Results
Acute oral toxicity Rat (Sprague-Dawley) PMRA #2179563	LD_{50} ♂ = 1635 mg/kg bw LD_{50} ♀ = 2015 mg/kg bw Slight acute toxicity Supplemental
Acute oral toxicity Rat (Sprague-Dawley) PMRA #2314228	LD_{50} ♂ = 3847 mg/kg bw LD_{50} ♀ = 2278 mg/kg bw Low acute toxicity
Acute Dermal Toxicity Rat (Sprague-Dawley) PMRA# 2314236	LD_{50} > 5000 mg/kg bw Low acute toxicity
Acute Inhalation Toxicity Rat (Fischer) PMRA# 2179566	LC_{50} > 4.57 mg/L Low acute toxicity
Eye Irritation Rabbit (NZW) PMRA# 2179568	MAS = 1.3 MIS = 10 (1h) Minimally irritating
Dermal Irritation Rabbit (NZW) PMRA# 2314243	MAS = 0 MIS = 1 (1h) Non-irritating
Dermal Sensitization Guinea Pig (Hartley) PMRA# 2179571	Non-sensitizing
Local Lymph Node Assay Mouse CBA/JNCrj PMRA# 2485744	Non-sensitizing

Study Type/Animal/PMRA #	Study Results
90-day oral (dietary) Rat (Sprague-Dawley) PMRA# 2179572	NOAEL = 13/16 mg/kg bw/day LOAEL = 70/81 mg/kg bw/day Effects at the LOAEL: ↑thyroid follicular cell hyperplasia; ↓fc, ↑wc, ↑thyroid wt, hepatocyte enlargement, ↑incidence of hyaline droplets and eosinophilic bodies in kidney, ↑ratio of basophilic cells in pituitary (♂); ↓ bw/bwg, ↑ liver wt, enlarged hepatocellular nuclei/nucleioli (♀)
90-day oral (capsule) Beagle dog PMRA# 2179576	NOAEL = 10 mg/kg bw/day LOAEL = 50 mg/kg bw/day Effects at the LOAEL: ↓bw/bwg, ↑ liver wt, ↑ homogenous hepatocytic cytoplasm; subdued mood, distended abdomen , ↑ALK , ↑ thyroid wt (♂)
107- week (capsule) Beagle dog PMRA# 2179599 PMRA# 2179600 PMRA# 2179601 PMRA# 2179602 PMRA# 2179603	NOAEL = 2 mg/kg bw/day LOAEL= 20 mg/kg bw/day Effects at the LOAEL: ↑ ALK, ↑ bile duct hyperplasia in the liver; ↑ enlargement of centriacinar region in the liver (♂); ↑ liver wt, ↑ mammary gland hyperplasia (♀)
24-day dermal Rats (Sprague-Dawley) PMRA# 2179577 PMRA# 2314245	<u>Systemic Toxicity</u> NOAEL = 1000 mg/kg bw/day (♂) NOAEL = 300 mg/kg bw/day (♀) Effects at the LOAEL: ↑ focal necrosis with inflammatory infiltrate of the liver (♀) <u>Dermal Irritation</u> NOAEL = 300 mg/kg bw/day LOAEL = 1000 mg/kg bw/day Effects at the LOAEL: ↑ hyperkeratosis and acanthosis, ↑ basal epithelial cell vacuolar degenerative change of the skin (♂); full spectrum inflammatory response of the skin (♀)
28-day inhalation Rats (Sprague-Dawley) PMRA 2523902	NOAEC = 0.1 mg/L LOAEC = 0.5 mg/L Effects at the LOAEC: ↑ liver wt, minimal grade centrilobular hypertrophy, ↑ triglycerides, slightly ↑ adrenocortical hypertrophy; ↓bw, ↓reticulocytes, ↑total protein, ↑globulin, ↓spleen wt (♂); ↑adrenal wt (♀)
90-day inhalation PMRA# 2314208	Waiver request granted on the basis of low vapour pressure, low acute toxicity, and achieved MOE for relevant exposure scenarios

Study Type/Animal/PMRA #	Study Results
24-month chronic toxicity / oncogenicity (dietary) Rat (Sprague-Dawley) PMRA# 2179594 PMRA# 2179595 PMRA# 2179596 PMRA# 2179597 PMRA# 2179598 PMRA# 2179579	NOAEL = 0.9/11 mg/kg bw/day (♂/♀) LOAEL = 8.7/115 mg/kg bw/day Effects at the LOAEL: ↑ liver and thyroid wt, enlargement of hepatocytes, ↑liver centrilobular hypertrophy, ↑ thyroid small follicles,↑ thyroid follicular cell hyperplasia and hypertrophy, ↑ proliferation of parafollicular cells, ↑ parafollicular cell hyperplasia; transient ↓ bw (first few weeks), enlargement of liver, thyroid, and pituitary, ↓ ALT, AST, ↑ thyroid follicular cell hypertrophy and hyperplasia, slight ↑ in small round cell infiltration of liver portal region, ↑ liver diffuse hypertrophy, enlarged reticulum cells in spleen (♂); ↓ bw/bwg, ↓ glucose, ↑ kidney wt, slight, non-statistically significant increase in incidence of hepatocellular adenomas, but no incidence of hepatocellular carcinomas in any groups, including controls, or indication of buprofezin-related tumorigenicity in ♂ Low level of concern for tumorigenic potential
24-month chronic toxicity / oncogenicity (dietary) Mouse (CD-1) PMRA# 2179580 PMRA#2179582 PMRA#2179585 PMRA#2179587 PMRA#2179589 PMRA#2179592 PMRA#2314226 PMRA#2314227	NOAEL = 17/18 mg/kg bw/day (♂/♀) LOAEL = 190/191 mg/kg bw/day Effects at the LOAEL: ↑ platelets, ↑ liver wt, ↑ centrilobular hepatocellular swelling, ↑ hepatocellular hyperplasia; ↑ adrenal wt (♂); ↑ total cholesterol, ↓ urine ketones, ↑ incidence of liver adenomas and combined liver adenomas/carcinomas [5/80, 4/80, 1/80, 11/80*](♀) *$p \leq 0.05$ Evidence of oncogenicity in ♀

Study Type/Animal/PMRA #	Study Results
Two-generation Reproductive Toxicity Study (diet) Rat (Wistar-Imamichi) PMRA# 2314232	Parental Toxicity NOAEL = 66/93 mg/kg bw/day (♂/♀) HDT LOAEL = not determined No adverse treatment-related findings Reproductive Toxicity NOAEL = 66/93 mg/kg bw/day (♂/♀) LOAEL = not determined No adverse treatment-related findings Offspring Toxicity NOAEL = 9.2 mg/kg bw/day LOAEL = 93 mg/kg bw/day Effects at the LOAEL: ↓ bwg PND 0-14, PND 0-21 (F_2) Evidence of sensitivity of the young
Developmental Toxicity (gavage) Rat (Sprague-Dawley) PMRA# 2179622 PMRA# 2179623	Maternal Toxicity NOAEL = 200 mg/kg bw/day LOAEL = 800 mg/kg/day Effects at the LOAEL: ↓ bw, ↓ bwg, ↓ fc, ↑wc, ↑ total litter loss, ↑ early and total resorptions, ↑ post-implantation loss, ↓ live fetuses, loose feces, urogenital staining, lethargy, hunched posture, thin appearance, piloerection, partial closure of the eyelids, 1 dam sacrificed *in extremis*. Developmental Toxicity NOAEL = 200 mg/kg bw/day LOAEL = 800 mg/kg bw/day Effects at the LOAEL: ↑ total litter loss, ↓ live fetuses, ↓ fetal wt, ↑ small fetus, ↑ space between body wall and organs, ↑ subcutaneous edema, incomplete ossification of 3 sternebrae, ↑ absence of 1st thoracic vertebral centrum, ↑ incomplete ossification of caudal vertebrae (less than 5 ossified), ↑ metacarpals/metatarsals 3/4, ↓ metacarpals/metatarsals 4/4 Serious effect in the presence of maternal toxicity.

Study Type/Animal/PMRA #	Study Results
Developmental Toxicity (gavage) Rabbit (New Zealand White) PMRA# 2179625 (study), 2314244 (sup.)	Maternal Toxicity NOAEL = 50 mg/kg bw/day LOAEL = 250 mg/kg bw/day Effects at the LOAEL: ↓ bw (GD 8, 14), ↓ bwg (loss GD 6-12; ↓ overall), ↓ fc, ↓ fecal output Developmental Toxicity NOAEL = 250 mg/kg bw/day (HDT) LOAEL = not determined No evidence of sensitivity of the young.
Gene mutation in bacteria *S.* Typhimurium TA98, TA100, TA1535, TA1537, TA1538 PMRA# 2179626	Negative
Gene mutation in bacteria *S.* Typhimurium TA98, TA100, TA1535, TA1537, TA1538 and *E.coli* WP2/uvrA PMRA# 2314246	Negative Supplemental
Mammalian gene mutation (in vitro) L5178Y mouse lymphoma cells PMRA#2179627	Negative
Micronucleus assay (*in vivo*) Mouse (BDF1) PMRA# 2179631	Doses tested: 6400, 8000, 10000 mg/kg bw Weak positive response in males and females following single administration, 24 hour sampling time. Negative response in both sexes following repeated dosing, all sampling times. Negative response in both sexes at all dose levels in repeat assay. Doses tested were well above the limit dose. Mortality (4/6 males) at high dose (repeated dosing only). Statistically significant increases observed in males at all dose levels and females at the high dose following single administration when sampled at 24 hours. Negative results in both sexes at all sampling times following repeated dosing. Negative results in both sexes at all dose levels following single administration in repeat assay

Study Type/Animal/PMRA #	Study Results
Micronucleus assay (*in vivo*) Mouse (Slc/ICR) PMRA# 2179630	Positive at 2000 mg/kg bw 2000 mg/kg bw: hypolocomotion Kinetochore analysis identified a slight increase (32%, not statistically significant) in the number of kinetochore positive micronuclei
Micronucleus assay (in vitro) Unscheduled DNA Synthesis Syrian hamster embryo cells PMRA# 2485747	Micronucleus assay – positive Unscheduled DNA synthesis - negative Kinetochore analysis identified an increase in the number of kinetochore positive micronuclei at the highest dose. It appears likely that the compound exerts its effects by interacting with the mitotic apparatus and acts as an aneuploidogen.
Chromosome aberration (in vitro) V79 CHL cell cultures PMRA# 2314237	Negative
Unscheduled DNA Synthesis Rat hepatocytes PMRA# 2179628	Negative
Chromosomal aberration (bone marrow cells and spermatocytes) Mouse (Swiss) PMRA# 2485748	Bone marrow cells- weakly clastogenic Spermatocytes- negative Supplemental. The test substance was a 25% SC formulation of buprofezin technical, the exact composition of which was not provided.
Acute Neurotoxicity PMRA # 2179621	Waiver rationale accepted on the basis of lack of neurotoxicity in the 90-day neurotoxicity study at doses that would have approximated those used in an acute neurotoxicity study, general lack of signs of neurotoxicity in the database (exception of ataxia in dogs at highest dose in 90-day study [300 mg/kg bw/day] which was not reproduced with 2-year dosing)

Study Type/Animal/PMRA #	Study Results
13-weeks Neurotoxicity (dietary) Rat (Sprague-Dawley) PMRA # 2179574	NOAEL = 35/43 mg/kg bw/day (♂/♀) HDT LOAEL = not determined No evidence of neurotoxicity
28-day immunotoxicity study (diet) Rat (Sprague-Dawley) PMRA #2179638	NOAEL = 78/79 mg/kg bw/day (♂/♀) LOAEL = 343/346 mg/kg bw/day Effects at the LOAEL: ↓bw/bwg, ↓fc, liver enlargement; ↑WC, ↓ spleen wt, ↓ anti-SRBC response for both PFC/spleen and PFC/10^6 viable cells (♀) Evidence of immune dysregulation
14-day oral (gavage) Rat (Sprague-Dawley) PMRA# 2314238	10 mg/kg bw/d: ↑ abs liver wt at 14 days ≥ 100 mg/kg bw/d: ↑ liver wt at 7 and 14 days, enlarged liver at 14 days, centrilobular hepatocellular hypertrophy at 7 and 14 days, follicular cell hypertrophy at 7 and 14 days, ↑TSH, ↑PROD activity (CYP2B1) at 7 and 14 days, ↑4NP-UDP-GT activity (reflects T4-UDP-GT conjugation) at 7 and 14 days. 500 mg/kg bw/d: ↑thyroid wt at 7 and 14 days, enlarged liver at 7 and 14 days, enlarged thyroid gland (discoloured area, reddish) at 7 and 14 days, follicular lumen hemorrhage at 7 and 14 days, ↓T3 at 3, 7, and 14 days, ↓T4 at 3, 7, and 14 days. Supplemental

Study Type/ Animal/PMRA #	Study Results
Mechanistic study to elucidate possible thyroidal MOA Rat (Sprague Dawley), mouse (ddY), guinea pigs (Hartley), rabbit (Japanese White) PMRA# 2485744	Test 1: ↓T3 after 4 doses via oral gavage in rats at 500 mg/kg bw, ↓T4 after 2 doses at 500 mg/kg bw Test 2: ↓T3 & T4 after dosing via oral gavage in rats with ≥300 mg/kg bw for 7 days (but no dose-response for T3) Test 3: ↓T3 after dietary administration to rats for 1 month at 5000 ppm, ↓T4 after 1 and 3 months with trend towards recovery to normal value with increased study duration Test 4: ↑rel thyroid wt after 15, 30 and 60 days of oral gavage dosing with 500 mg/kg bw/day in rats, ↓T4 (however T4 levels gradually increased as study time period progressed), ↑TPO (levels increased at Day 15, then recovered to normal at Day 30, then increased again at Day 60), ↑pituitary vacuolation Direct effect of buprofezin on TPO: In vitro incubation of TPO with buprofezin showed no effect on TPO activity (in comparison, potassium cyanide and PTU completely inhibited TPO). Species differences in serum concentrations of T4: Dose-related ↓in T4 was shown to correlate with protein-bound iodine (PBI) in rats treated with buprofezin. PBI was also measured as a surrogate for T4 in mice, hamsters and guinea pigs. Repeated doses in rats, mice and guinea pigs at 300 and 500 mg/kg bw/day (mice, up to 1000 mg/kg bw/day) did not significantly alter PBI concentrations. In rabbits treated with 300 or 1000 mg/kg bw/day, ↓ PBI was observed from Day 2. Supplemental

Study Type/ Animal/PMRA #:	Study Results:
Developmental thyroid toxicity range-finding study (gavage) Rat (Sprague-Dawley) PMRA# 2314242	Maternal Toxicity 300 mg/kg bw/day (HDT): No effects noted on body weight, food consumption, clinical signs, mortality, pup delivery and nursing behavior Offspring Toxicity 300 mg/kg bw/day (HDT): ↓body weight at PND 5 and all time points assessed to PND 21 in pups exposed in utero and gavage-dosed from PND 6-21 as well as pups exposed in utero but remaining untreated over the postnatal period; ↑rel liver and thyroid wt, ↑incidence of centrilobular hepatocyte hypertrophy, ↑incidence hepatocyte vacuolation, ↑thyroid follicular cell hypertrophy ↓colloid area of thyroid in gavage-dosed pups Non-pregnant Adult Female Toxicity ≥100 mg/kg bw/d: ↑ liver and thyroid wt, ↑hepatocyte hypertrophy, ↑incidence of follicular cell hypertrophy, ↓colloid area of thyroid follicular cells [liver, thyroid, pituitary wts as well as histopathology of these organs conducted on non-pregnant ♀ only] No effect on the pituitary gland in pups or non-pregnant animals No evidence of hyperplasia in the thyroid gland Supplemental – dose-range finding study

Study Type/ Guideline/ PMRA #/	Study Results
Developmental thyroid toxicity study (gavage) – Non-Guideline Rat (Sprague-Dawley) PMRA# 2523900	Maternal Toxicity NOAEL = 10 mg/kg bw/day LOAEL = 80 mg/kg bw/day Effects at the LOAEL: ↑ TSH, ↑ liver wt, ↑ thyroid wt, ↑ thyroid follicular cell height, ↓ thyroid colloid area, ↑ thyroid follicular cell hypertrophy, ↑ liver centrilobular hypertrophy, ↑ hepatocyte vacuolation Fetal Toxicity – (GD 20) NOAEL = 10 mg/kg bw/day (equivocal ↑thyroid wt) LOAEL = 80 mg/kg bw/day Effects at the LOAEL: ↑ thyroid weight (♂), ↑ TSH (♂) Offspring Toxicity – Weaned Pups and Culled Pups NOAEL not established as effects occurred down to the lowest dose tested LOAEL = 10 mg/kg bw/day Pups directly dosed (PND 7-21) Effects at the LOAEL: ↓ bw (PND 4-7 before direct dosing), ↓ bwg (PND 0-7), ↑ TSH (♂) Pups not directly dosed (PND 7-21): Effects at the LOAEL: ↓ bw (LD 7) Culled pups (on PND 4) Effects at the LOAEL: ↑ TSH (♂) Non-pregnant Adult Female Toxicity NOAEL = 10 mg/kg bw/day LOAEL = 80 mg/kg bw/day Effects noted at the LOAEL: ↑ TSH, ↑ liver wt, ↑ thyroid follicular cell height, ↓ thyroid colloid area, ↑ thyroid follicular cell hypertrophy, ↑ liver centrilobular hypertrophy Evidence of sensitivity of the young
Acute Oral Toxicity (Acute Toxic Class) BF 4 Metabolite Rat (Sprague-Dawley) PMRA # 2179962	LD_{50} = 300-2000 mg/kg bw 300 mg/kg bw: soiled fur, lacrimation, diarrhea 2000 mg/kg bw: soiled fur, lying on side, decrease/loss of locomotor activity, rales, death (day 1)

Study Type/ Guideline/ PMRA #	Study Results
Gene mutation in bacteria DIF-8 Metabolite *S. Typhimurium* TA98, TA100, TA1535, TA1537, *E. coli* WP2 uvrA PMRA #2331/2234	Negative
Acute Oral Toxicity (Acute Toxic Class) DIF-26 Metabolite Rat (Sprague-Dawley) PMRA # 2179961	LD_{50} = 501-1000 mg/kg bw 501 mg/kg bw: no clinical signs 1000 mg/kg bw: soiled fur around mouth, lying on side, convulsion, death (< 1/3 min)
Gene mutation in bacteria DIF-26 Metabolite *S. Typhimurium* TA98, TA100, TA1535, TA1537, *E. coli* WP2 uvrA PMRA #2331/2233	Negative
28-day oral toxicity study DIF-26 Metabolite Rat (Fischer) PMRA #: 2471214	NOAEL = 75 mg/kg bw/day 75 mg/kg bw/day (HDT): slight ↑total cholesterol, reddish spots on thyroid (1/5 ♂), very slight hemorrhage in thyroid follicular lumen (1/5 ♂), very slight ↑APTT (♂)

Table 9 Toxicological Endpoints Selected for Human Health Risk Assessment

Exposure Scenario	Study	Point of Departure and Endpoint	UF[1] or Target MOE
Acute dietary (general population)	Co-critical studies 90-day oral (capsule) toxicity study in dogs. Gavage developmental toxicity study in rabbits	NOAEL = 50 mg/kg bw Anemia (dog), decreased body weight and body weight gain (rabbit)	100
	ARfD = 0.5 mg/kg bw of bupirobam		

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Acute dietary females aged 13-49	Not required		
Repeated dietary	24-month chronic toxicity/oncogenicity study in rats	NOAEL = 1.0 mg/kg bw/day Increased incidence of thyroid follicular cell hypertrophy and hyperplasia	100
	ADI = 0.01 mg/kg bw/day of buprofezin		
Short- to intermediate-term dermal[2]	Developmental toxicity study in rats	LOAEL = 10 mg/kg bw/day Decreased pup body weight and body weight gain, and increased TSH	100
Short- to intermediate term inhalation[3]	Developmental thyroid toxicity study in rats	LOAEL = 10 mg/kg bw/day Decreased pup body weight and body weight gain, and increased TSH	100
Long-term dermal[2] and inhalation[3]	24-month chronic toxicity / oncogenicity study in rats	NOAEL = 1.0 mg/kg bw/day Increased incidence of thyroid follicular cell hypertrophy and hyperplasia	100
Cancer	24-month chronic toxicity / oncogenicity study in mice	q_1^* of 2.3×10^{-3} (mg/kg bw/day) $^{-1}$, based on the combined incidence of liver adenomas / carcinomas in female mice	

[1] *CAF (composite assessment factor)* refers to a total of uncertainty and *Pest Control Products Act* factors for dietary assessments. MOE refers to a target MOE for occupational assessments.
[2] Since an oral NOAEL was selected, a dermal absorption factor of 50% was used in a route-to-route extrapolation.
[3] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation.

Table 6 Dermal Exposure for M/L/As handling Applaud Insect Growth Regulator: Dry Flowable, Open M/L + Liquid Open Pour, M/L/A (Single layer with gloves)

Scenario	Application Rate (g a.i./L)[1]	ATPD (L/day)	Unit Exposure (µg/kg a.i. handled)[2]	Dermal Exposure (mg/kg bw/day)[3]	Dermal MOE[4]	
Mechanically-pressurized handgun	0.3	3800	5749.25	0.04096	244	
Manually-pressurized handwand		150	1107.14	0.00031	32115	
Backpack		150	5609.62	0.00158	6338	

[1] Application Rate (g a.i./L) = Application Rate (g product/100L) × Guarantee (30%)
[2] PHED Unit exposure values for single layer with gloves
[3] Dermal Exposure (mg/kg bw/day) = Application Rate (g a.i./L) × Conversion Factor (kg/1000g) × ATPD (L/day) ÷ Unit

Exposure (µg/kg a.i. handled) ÷ Dermal Absorption Factor (50%) ÷ Body Weight (80 kg)
[4] Calculated MOE = LOAEL of 10 mg/kg bw/day ÷ Dermal Exposure (mg/kg bw/day); Target MOE = 100

Table 7 Inhalation Exposure for M/L/As handling Applaud Insect Growth Regulator: Dry Flowable, Open M/L ÷ Liquid Open Pour, M/L/A

Scenario	Inhalation Unit Exposure (µg/kg a.i. handled)[1]	Inhalation Exposure (mg/kg bw/day)[2]	Inhalation MOE[3]	Combined MOE[4]	
Mechanically-pressurized handgun	152.02	0.002166	4620	232	
Manually-pressurized handwand	46.22	2.6×10^{-5}	385000	29600	
Backpack	63.12	3.55×10^{-5}	282000	6200	

[1] Inhalation exposure is moderate for the backpack scenario but light for the other scenarios.
[2] Inhalation Exposure (mg/kg bw/day) = Application Rate (g a.i./L) × ATPD (L/day) × Unit Exposure (µg/kg a.i. handled) × Inhalation Absorption Value (100%) ÷ Body Weight (80 kg)
[3] MOE = LOAEL of 10 mg/kg bw/day ÷ Inhalation Exposure (mg/kg bw/day); Target MOE = 100
[4] Combined MOE = $1 \div ((1/MOE_{Dermal}) + (1/MOE_{Inhalation}))$; Target MOE = 100

Table 8 Mixer/Loader/Applicator Dermal and Inhalation Cancer Risk Assessment

Scenario	ADD (mg/kg bw/day)[1]	LADD (mg/kg bw/day)[2]	Cancer Risk[3]
Mechanically-pressurized hand-held equipment	0.0431	1.82×10^{-3}	4.2×10^{-6}
Manually-pressurized handwand	0.000337	1.42×10^{-5}	3.3×10^{-8}
Backpack	0.00161	6.80×10^{-5}	1.6×10^{-7}

[1] Absorbed Daily Dose (ADD) (mg/kg bw/day). To calculate ADD, the dermal and inhalation exposure values (mg/kg bw/day) were summed.
[2] $LADD = \frac{ADD \times \text{Treatment Frequency (days per year)} \times \text{Duration of Exposure (years)}}{365 \text{ days/year} \times \text{Life Expectancy (years)}}$
[3] Cancer Risk = LADD (mg/kg bw/day) × q_1^* (mg/kg bw/day)$^{-1}$

Table 9 Post-Application Dermal Exposure and Risk Estimates to Applaud Insect Growth Regulator on Day 0 after Application to Ornamentals (Excluding Cut Flowers), Greenhouse Groundcover and Landscape Plants and Day 2 after Application to Greenhouse Vegetables (Peppers, Tomatoes And Cucumbers)

Crop	Application Rate ($\mu g/cm^2$)	TC (cm^2/hr)	Peak DFR ($\mu g/cm^2$) [1]	Maximum Number of Applications per Crop Cycle	Dermal exposure (mg/kg bw/day) [3]	MOE[4]
Greenhouse Ornamentals	3	230	0.7500	1	0.0086	116
Greenhouse Vegetables	2.2	1400	0.1391	2	0.0097	103

[1] Calculated for greenhouse ornamentals (excluding cut flowers), greenhouse ground cover and landscape plants using the dislodgeable residue default of 25% and dissipation per day of 0% and for greenhouse vegetables using chemical-specific DFR data.

[2] Exposure = (Peak DFR [$\mu g/cm^2$] × TC [cm^2/hr] × 8 hours × 50% dermal absorption) ÷ (80 kg bw × 1000 µg/mg)

[3] Based on a NOAEL of 1 mg/kg bw/day, target MOE = 100 (see Table 2)

Table 10 Re-entry Worker Dermal Cancer Risk Assessment

Scenario	Application Rate ($\mu g/cm^2$)	TWA DFR ($\mu g/cm^2$) [1]	ADD (mg/kg bw/day) [2]	LADD (mg/kg bw/day) [3]	Cancer Risk [4]
Greenhouse Ornamentals	3	0.750	0.00863	0.000364	8.4×10^{-7}
Greenhouse Vegetables	2.2	0.0758	0.00522	0.00022	5.1×10^{-7}

[1] The TWA of DFR values over the 30 day period after the first application.

[2] Absorbed Daily Dose (ADD) (mg/kg bw/day) = TWA DFR ($\mu g/cm^2$) × TC (cm^2/hr) × Hours Worked per Day (8 hrs/day) ÷ Body Weight (80 kg bw) × Dermal Absorption Factor (50%) ÷ Conversion Factor (1000 µg/mg)

[3] LADD = ADD (mg/kg bw/day) × Treatment Frequency (days/year) × Duration of Exposure (years/lifetime) ÷ 365 days/year ÷ Life Expectancy (years/lifetime)

[4] Cancer Risk = LADD (mg/kg bw/day) × q_1^* (mg/kg bw/day)$^{-1}$

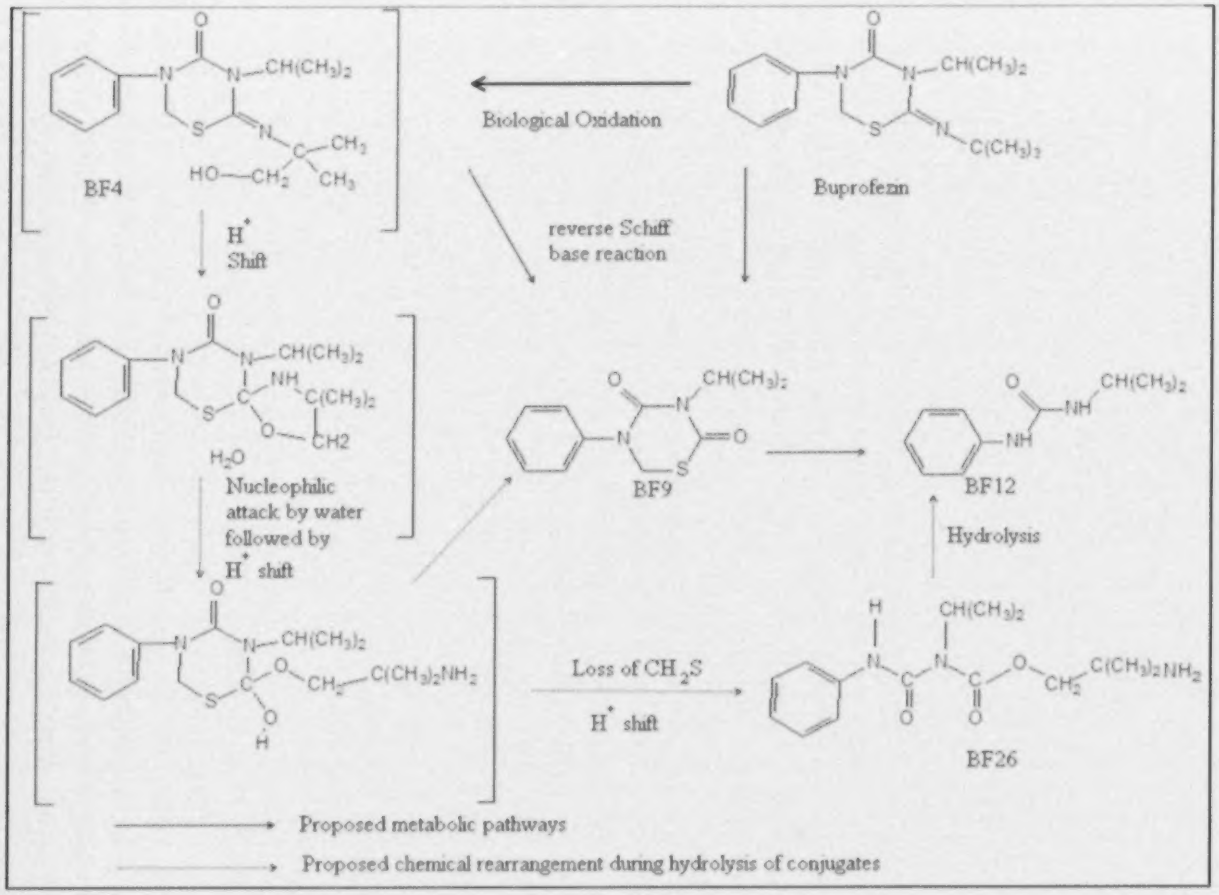
Table 11 Residue Analysis

Matrix	Method ID	Analyte	Method Type	LOQ	Reference
Plant	BF/10/07	Buprofezin	GC-NPD (quantitation) & GC-MS (confirmation)	0.05 ppm almond, orange, cottonseed, grape, banana, tomato	PMRA # 2179952
	BF/10/97, BF/10/07	Buprofezin, BF 9, BF 12	GC-NPD	0.05 ppm almond, cottonseed, lemons, grapes	PMRA # 2180307

Table 12 Integrated Food Residue Chemistry Summary

NATURE OF THE RESIDUE IN LETTUCE		PMRA # 2180298
Radiolabel Position	[U-14C-phenyl]-Buprofezin	
Test Site	Contained outdoor plots	
Treatment	Foliar treatment	
Total Rate	2 × 852 g a.i./ha; total rate of 1702 g a.i./ha	
Formulation	Suspension concentrate (SC) formulation	
Preharvest interval	14 days	
Matrices	[U-14C-phenyl]-Buprofezin	
	TRRs (ppm)	
Lettuce leaves	51.79	
Metabolites Identified	Major Metabolites (>10% of the TRRs)	Minor Metabolites (<10% of the TRRs)
Radiolabel Position	[U-14C-phenyl]-Buprofezin	
Lettuce leaves	Buprofezin	BF 9, BF 12, BF 26
NATURE OF THE RESIDUE IN TOMATO		PMRA # 2180301
Radiolabel Position	[U-14C-phenyl]-Buprofezin	
Test Site	Greenhouse	
Treatment	Foliar treatment	
Total Rate	4 applications of a 75 mg ai/L solution until runoff	
Formulation	Suspension concentrate (SC) formulation	
Preharvest interval	7 days	
Matrices	[U-14C-phenyl]-Buprofezin	
	TRRs (ppm)	
Tomato fruit	0.353	
Metabolites Identified	Major Metabolites (>10% of the TRRs)	Minor Metabolites (<10% of the TRRs)
Radiolabel Position	[U-14C-phenyl]-Buprofezin	
Tomato fruit	Buprofezin	-
NATURE OF THE RESIDUE IN LEMON		PMRA # 2180297
Radiolabel Position	[U-14C-phenyl]-Buprofezin	
Test Site	Greenhouse	
Treatment	Foliar treatment	
Total Rate	2 × 500 g a.i./ha; total rate of 1000 g a.i./ha	
Formulation	Suspension concentrate (SC) formulation	
Preharvest interval	14 days	
Matrices	[U-14C-phenyl]-Buprofezin	
	TRRs (ppm)	
Lemon pulp	<0.01	
Lemon peel	0.843	

Metabolites Identified	Major Metabolites (>10% of the TRRs)	Minor Metabolites (<10% of the TRRs)
Radiolabel Position	[U-14C-phenyl]-Buprofezin	
Lemon peel	Buprofezin	BF 9, BF 12, BF 26
NATURE OF THE RESIDUE IN COTTONSEED		PMRA # 2180299
Radiolabel Position	[U-14C-phenyl]-Buprofezin	
Test Site	Contained outdoor plots	
Treatment	Foliar treatment	
Total Rate	2 × 852 g a.i./ha; total rate of 1702 g a.i./ha	
Formulation	Suspension concentrate (SC) formulation	
Preharvest interval	27 days	
Matrices	[U-14C-phenyl]-Buprofezin	
	TRRs (ppm)	
Gin trash	14.01	
Cottonseeds	0.30	
Metabolites Identified	Major Metabolites (>10% of the TRRs)	Minor Metabolites (<10% of the TRRs)
Radiolabel Position	[U-14C-phenyl]-Buprofezin	
Gin trash	Buprofezin	BF 9, BF 12, BF 26
Cottonseed	Buprofezin	BF 9, BF 12, BF 26
Proposed Metabolic Scheme in Plants Buprofezin is biologically oxidized to BF 4, which is most likely hydrolyzed to BF9, BF12, and BF26. It is reported that BF4 is unstable, and can only be de-conjugated with the concomitant formation of BF9, BF12, and BF26.		



FREEZER STORAGE STABILITY	PMRA # 2180313, 2180314, 2180318, 2180343, 2180315

Plant matrices:
Bananas, potatoes, wheat (grain, forage, hay, and straw), almond (hulls and nutmeat), orange juice, lettuce, whole tomatoes, and tomato (fruit, juice, dry pomace, paste)
The freezer storage stability data indicate that residues of buprofezin, BF 9, and BF 12 are stable at -20°C for the durations tested (70-957 days), with the exception of wheat (grain, forage, hay, and straw) which showed decline of BF 9 and BF 12 over 874 days.
Grape (fruit, raisins), orange oil, apple, cotton (seed, refined oil)
The freezer storage stability data indicate that residues of buprofezin are stable at -10 to -20oC for the durations tested (180-1429 days).
In addition to the freezer storage stability studies cited above, several crop field trials included freezer storage stability data.

CROP FIELD TRIALS & RESIDUE DECLINE ON AVOCADO										PMRA # 2180393
Field trials were conducted in 2000 in the United States and Puerto Rico. All trials were conducted in NAFTA Growing Regions 3 (3 trials) and 13 (1 trial). Applaud 70 WP was to be applied twice as foliar broadcast sprays at a rate of 1770 g a.i./ha/application for a nominal seasonal application rate of 3540 g a.i./ha. For three trials conducted in Florida, there was an application that occurred too early, 63-124 days before the first of two applications. Therefore, the actual application rates for the four trials were 3540-5310 g ai/ha. The last two applications were made at 12-15-day intervals. For all trials, the last application occurred approximately 21-23 days before harvest.										
Commodity	Total Application Rate (g a.i./ha)	PHI (days)	Buprofezin Residue Levels (ppm)							
			n	Min.	Max.	LAFT	HAFT	Median	Mean	SD
Avocado	3540-5310	21-23	8	<0.02	0.232	<0.02	0.197	0.035	0.081	0.081
CROP FIELD TRIALS & RESIDUE DECLINE ON BANANA										PMRA # 2180344, 2180375
Field trials were conducted in 1996 and in 2003 in the United States. Trials were conducted in NAFTA Growing Regions 3 (1 trial) and 13 (5 trials). Applaud 70WP was applied four times as foliar broadcast sprays at a rate of 347 g a.i./ha/application for a seasonal application rate of 1389 g a.i./ha. Applications were made at 14-day intervals. The last application occurred approximately 1 day before harvest. Residue decline data show that residues of buprofezin increased slightly in bananas with increasing preharvest intervals (PHIs).										
Commodity	Total Application Rate (g a.i./ha)	PHI (days)	Buprofezin Residue Levels (ppm)							
			n	Min.	Max.	LAFT	HAFT	Median	Mean	SD
Banana (unbagged)	1389	1	12	<0.01	0.177	0.015	0.175	0.049	0.046	0.020
		3	2	0.02	0.03	-	-	-	0.025	-
		7	2	0.03	0.14	-	-	-	0.085	-
		14	2	0.03	0.04	-	-	-	0.035	-
Residues of BF 9 and BF 12 were each <0.01 ppm in all samples.										
CROP FIELD TRIALS & RESIDUE DECLINE ON SNAP BEANS										PMRA # 2180392
Field trials were conducted in 2000 in the United States. Trials were conducted in NAFTA Growing Regions 1(1 trials), 2 (1 trial), 3 (1 trial), 5 (3 trials), and 11 (1 trial). Applaud 70WP was applied twice as foliar broadcast sprays at a rate of 419-442 g a.i./ha/application for a seasonal application rate of 849-883 g a.i./ha. Applications were made at 10-15-day intervals. The last application occurred approximately 9-34 days before harvest.										
Commodity	Total Application Rate (g a.i./ha)	PHI (days)	Buprofezin Residue Levels (ppm)							
			n	Min.	Max.	LAFT	HAFT	Median	Mean	SD
Snap beans	849-883	9-34	14	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	-

CROP FIELD TRIALS & RESIDUE DECLINE ON LOW GROWING BERRIES CSG 13-07G (STRAWBERRIES)	PMRA # 2180370

Field trials were conducted in 2003 and in 2004 in the United States. Trials were conducted in NAFTA Growing Regions 2 (3 trials), 3 (1 trial), 5 (1 trial), 10 (3 trials), and 12 (1 trial). Courier 40 SC was applied twice as foliar broadcast sprays at a rate of 375-399 g a.i./ha/application for a seasonal application rate of 757-792g a.i./ha. Applications were made at 6-10-day intervals. The last application occurred approximately 2-4 days before harvest.

Residue decline data show that residues of buprofezin decreased in strawberries with increasing preharvest intervals (PHIs).

Commodity	Total Application Rate (g a.i./ha)	PHI (days)	Buprofezin Residue Levels (ppm)							
			n	Min.	Max.	LAFT	HAFT	Median	Mean	SD
Strawberries	757-792	2-4	18	0.10	1.2	0.37	1.15	0.44	0.58	0.31
		1	4	0.48	1.4	0.50	1.3	0.86	0.90	0.47
		4	4	0.40	0.85	0.48	0.85	0.70	0.66	0.23
		7	4	0.26	0.80	0.29	0.69	0.45	0.49	0.25
		10	4	0.25	0.34	0.26	0.34	0.30	0.30	0.04

CROP FIELD TRIALS & RESIDUE DECLINE ON BRASSICA HEAD AND STEM CSG 5A (BROCCOLI & CABBAGE)	PMRA # 2180386

Field trials were conducted in 2007 in the United States. Trials were conducted in NAFTA Growing Regions 6 (1 trials), 10 (4 trials), and 12 (1 trial) for broccoli and in Regions 1 (1 trial), 2 (1 trial), 3 (1 trial), 5 (1 trial), 6 (1 trial), and 10 (1 trial) for cabbage. At each trial location, Courier 40 SC was applied twice as foliar broadcast sprays at a nominal rate of 420 g a.i./ha/application for a nominal seasonal application rate of 840 g a.i./ha. Applications were made at 8-day intervals. The last application occurred 1 day before harvest.

Residue decline data show that residues of buprofezin decreased in cabbage with increasing preharvest intervals (PHIs).

Commodity	Total Application Rate (g a.i./ha)	PHI (days)	Buprofezin Residue Levels (ppm)							
			n	Min.	Max.	LAFT	HAFT	Median	Mean	SD
Broccoli	840	1	12	0.674	1.56	0.84	1.38	1.01	1.04	0.28
Cabbage		1	12	0.336	4.51	0.378	4.00	1.82	2.03	1.35
		0	2	0.362	0.404	-	-	-	0.386	-
		1	2	0.336	0.419	-	-	-	0.378	-
		5	2	0.297	0.391	-	-	-	0.344	-
		10	2	0.139	0.286	-	-	-	0.213	-

Residues of BF 9 and BF 12 were each <0.01 ppm in all samples.

CROP FIELD TRIALS & RESIDUE DECLINE ON BRASSICA LEAFY GREEN CSG 5B (MUSTARD GREENS)	PMRA # 2180366

Field trials were conducted in 2008 in the United States. Trials were conducted in NAFTA Growing Regions 2 (2 trials), 3 (1 trial), and 10 (2 trials). Courier 40 SC was applied twice as foliar broadcast sprays at a rate of 421-440 g a.i./ha/application for a seasonal application rate of 878-973 g a.i./ha. Applications were made at 5-7-day intervals. The last application occurred 1 day before harvest.

Commodity	Total Application Rate (g a.i./ha)	PHI (days)	Buprofezin Residue Levels (ppm)							
			n1	Min.	Max.	LAFT	HAFT	Median	Mean	SD
Mustard greens	878-973	1	10	7.67	40.9	8.7	34.9	18.8	19.1	10.1

CROP FIELD TRIALS & RESIDUE DECLINE ON COFFEE	PMRA # 2180374

Field trials were conducted in 2004 in the United States. Trials were conducted in NAFTA Growing Region 13 (5 trials). Applaud 70WP was applied four times as foliar broadcast sprays at a rate of 1120-1176 g a.i./ha/application for a seasonal application rate of 4514-5712 g a.i./ha. Applications were made at 14-day intervals. The last application occurred on the day of harvest. Harvested coffee cherries were dried for 2 days at the trial sites to produce green beans.

Commodity	Total Application Rate (g a.i./ha)	PHI (days)	Buprofezin Residue Levels (ppm)							
			n1	Min.	Max.	LAFT	HAFT	Median	Mean	SD
Coffee green beans	4514-5712	0	9	0.059	0.239	0.080	0.239	0.124	0.130	0.053

CROP FIELD TRIALS & RESIDUE DECLINE ON COTTONSEED	PMRA # 2180334, 2180383

Field trials were conducted in 1995 in the United States. Trials were conducted in NAFTA Growing Regions 2 (1 trial), 3 (1 trial), 4 (4 trials), 6 (2 trials), 8 (4 trials), 9 (1 trial), and 10 (2 trials). Applaud 70 WP was applied four times as foliar broadcast sprays at a nominal rate of 426 g a.i./ha/application for a nominal seasonal application rate of 1702 g a.i./ha. Applications were made at 5-day intervals. The last application occurred 14, 20-22, and 28 days before harvest.

Commodity	Total Application Rate (g a.i./ha)	PHI (days)	Buprofezin Residue Levels (ppm)							
			n1	Min.	Max.	LAFT	HAFT	Median	Mean	SD
Cottonseed	1702	14	15	0.06	0.82	0.06	0.82	0.21	0.32	0.28
		20-22	14	0.01	0.38	0.01	0.38	0.07	0.11	0.28
		28	2	0.04	0.16	0.04	0.16	-	0.10	-

Residues of BF 9 and BF 12 were each <0.01 ppm in all samples.

CROP FIELD TRIALS & RESIDUE DECLINE ON ORANGE CSG 10-A (ORANGE)	PMRA # 2180321

Field trials were conducted in 2000 in the United States. Trials were conducted in NAFTA Growing Regions 3 (12 trials), 6 (1 trial), 6 (1 trial), and 10 (4 trials). Applaud 70 WP was applied twice by airblast at a rate of 2240 g a.i./ha/application for a seasonal application rate of 4480-4510 g a.i./ha. Applications were made at 21-day intervals. The last application occurred 3 days before harvest.

Residue decline data show that residues of buprofezin decreased in oranges with increasing preharvest intervals (PHIs).

Commodity	Total Application Rate (g a.i./ha)	PHI (days)	Buprofezin Residue Levels (ppm)							
			n1	Min.	Max.	LAFT	HAFT	Median	Mean	SD
Orange	4480-4510	3	30	0.368	2.091	0.393	1.796	1.285	1.223	0.44
		1	4	1.313	1.945	1.427	1.629	1.427	1.528	0.29
		3	4	0.876	1.806	0.998	1.702	1.389	1.350	0.43
		5	4	0.877	1.845	0.959	1.743	1.287	1.324	0.49
		15	4	0.459	1.693	0.539	1.671	1.100	1.088	0.67

		30	4	0.204	0.667	0.295	0.601	0.434	0.435	0.21

Residues of BF 9 and BF 12 were <0.05 ppm in all samples except one residue decline trial where residues of BF 9 ranged from 0.052-0.108 ppm at PHI's of 5-30 days.

CROP FIELD TRIALS & RESIDUE DECLINE ON POME FRUITS CG 11-09 (APPLES AND PEARS) | **PMRA # 180391, 2180395**

Field trials were conducted in 2001 in the United States.

Apple trials were conducted in NAFTA Growing Regions 1(3 trials), 2 (1 trial), 5 (2 trials), 9 (1 trial), 10 (1 trial), and 11 (4 trials). Applaud 70 WP was applied once to apples as a foliar application at a rate of 1680 g a.i./ha, and harvest was 14-15 days later.

Pear trials were conducted in NAFTA Growing Regions 2 (1 trial), 8 (1 trial), 11 (3 trials), and 10 (3 trials). Applaud 70 WP was applied twice as a foliar application at 1770 g a.i./ha/application, for a seasonal application rate of 3539 g a.i./ha. Pears were harvested 13-15 days after the last application.

Commodity	Total Application Rate (g a.i./ha)	PHI (days)	Buprofezin Residue Levels (ppm)							
			n	Min.	Max.	LAFT	HAFT	Median	Mean	SD
Apple	1680	14-15	24	<0.10	0.99	<0.10	0.93	0.23	0.38	0.30
Pear	3539	13-15	16	0.31	3.64	0.36	3.17	0.76	1.08	0.88

CROP FIELD TRIALS & RESIDUE DECLINE ON STONE FRUITS CG 12-09 (PEACH, PLUM, CHERRY) | **PMRA # 2180369, 2180390, 2180394**

Field trials were conducted in 2002 in the United States for plums. Trials were conducted in NAFTA Growing Regions 5 (1 trial), 10 (4 trials), and 12 (1 trial). Applaud 70 WP was applied twice as foliar broadcast application at a rate of 1764-1792 g a.i./ha/application for a seasonal application rate of 3536-3575 g a.i./ha. Applications were made at 14-15-day intervals. The last application occurred approximately 13-14 days before harvest.

Field trials were conducted in 2000-2001 in the United States for peaches. Trials were conducted in NAFTA Growing Regions 2 (3 trials), 3 (1 trial), 4 (1 trial), 5 (1 trial), 6 (1 trial), and 10 (4 trials). Applaud 70 WP was applied twice as foliar broadcast applications at a rate of 1770 g a.i./ha/application for a seasonal application rate of 3540 g a.i./ha. Applications were made at 12-16-day intervals. The last application occurred approximately 13-15 days before harvest.

Field trials were conducted in 2002-2003 in the United States for cherries (tart and sour). Trials were conducted in NAFTA Growing Regions 2 (1 trial), 5 (6 trials), 9 (1 trial), 10 (2 trials), and 11 (3 trials). Applaud 70 WP was applied twice as foliar broadcast applications at a rate of 1726-1872 g a.i./ha/application for a seasonal application rate of 3470-3696 g a.i./ha. Applications were made at 13-15-day intervals. The last application occurred 12-14 days before harvest.

Commodity	Total Application Rate (g a.i./ha)	PHI (days)	Buprofezin Residue Levels (ppm)							
			n	Min.	Max.	LAFT	HAFT	Median	Mean	SD
Plum	3536-3575	12	12	0.05	0.548	0.050	0.492	0.151	0.194	0.16
Peach	3540	22	22	0.11	8.13	0.12	6.86	1.03	1.58	1.88
Cherry	3470-3696	25	25	0.30	1.32	0.31	1.17	0.57	0.69	0.31

CROP FIELD TRIALS & RESIDUE DECLINE ON GRAPES	PMRA # 2180333, 2180384, 2180385, 2180387

Field trials were conducted in 1996 in the United States on grapes. Trials were conducted in NAFTA Growing Regions 1 (3 trials), 10 (9 trials), and 11 (3 trials). Applaud 70 WP was applied twice as foliar broadcast application at a nominal rate of 560 g a.i./ha/application for a seasonal application rate of 1120 g a.i./ha. Applications were made at 14-day intervals. The last application occurred 30 days before harvest.

Field trials were conducted in 2004 and in 2008 in the United States. Trials were conducted in NAFTA Growing Regions 1(2 trials), 10 (8 trials), and 11 (2 trials). Applaud 70 WP/Courier WP were applied twice as foliar broadcast applications at a nominal rate of 560 g a.i./ha/application for a seasonal application rate of 1120 g a.i./ha. Applications were made at 14-day intervals. The last application occurred approximately 7 days before harvest.

One residue decline trial was conducted in 2008 in the United States. Trials were conducted in NAFTA Growing Region 10 (1 trials). Applaud DF was applied twice as foliar broadcast applications at a nominal rate of 560 g a.i./ha/application for a seasonal application rate of 1120 g a.i./ha.

Commodity	Total Application Rate (g a.i./ha)	PHI (days)	Buprofezin Residue Levels (ppm)							
			n1	Min.	Max.	LAFT	HAFT	Median	Mean	SD
Grapes	1120	7	24	0.043	0.743	0.043	0.709	0.158	0.237	0.20
		30	30	0.010	0.270	0.010	0.240	0.050	0.072	0.06
		3	2	0.152	0.225	-	-	-	0.189	-
		7	2	0.126	0.139	-	-	-	0.133	-
		14	2	0.076	0.105	-	-	-	0.090	-
		21	2	0.049	0.066	-	-	-	0.058	-
		30	2	0.033	0.063	-	-	-	0.048	-

Residues of BF 9 and BF 12 were each <0.01 ppm in all samples, except for the following. For the 30 day PHI, 12 samples showed residues at 0.01-0.02 ppm, the remaining 18 samples were <0.01 ppm.

CROP FIELD TRIALS & RESIDUE DECLINE ON LEAFY VEGETABLE, EXCEPT BRASSICA CG 4 (HEAD LETTUCE, LEAF LETTUCE, CELERY, SPINACH)	PMRA # 21601326, 21601000, 21601001

Field trials were conducted in 1998 in the United States for head lettuce. Trials were conducted in NAFTA Growing Regions 1 (2 trials), 5 (1 trial), 8 (1 trial), 9 (1 trial), and 10 (4 trials). Applaud 70 SC was applied four times as foliar broadcast application at a nominal rate of 426 g a.i./ha/application for a seasonal application rate of 1702 g a.i./ha. Applications were made at 5-day intervals. The last applications occurred 7 days before harvest.

Field trials were conducted in 1998 in the United States for leaf lettuce. Trials were conducted in NAFTA Growing Regions 1(1 trial), 3 (2 trials), 8 (1 trial), and 10 (3 trials). Applaud 70 SC was applied four times as foliar broadcast application at a nominal rate of 426 g a.i./ha/application for a seasonal application rate of 1702 g a.i./ha. Applications were made at 5-day intervals. The last application occurred 7 days before harvest.

Field trials were conducted in 2004 in the United States for celery. Trials were conducted in NAFTA Growing Regions 1 (1 trial), 5 (1 trial), and 10 (4 trials). Courier SC was applied twice as foliar broadcast applications at a rate of 426 g a.i./ha/application for a seasonal application rate of 852g a.i./ha. Applications were made at 7-day intervals. The last application occurred 7 days before harvest.

Field trials were conducted in 2004 in the United States for spinach. Trials were conducted in NAFTA Growing Regions 1 (1 trial), 2 (1 trial), 8 (1 trial), and 10 (3 trials). Courier SC was applied twice as foliar broadcast applications at a nominal rate of 426 g a.i./ha/application for a seasonal application rate of 852 g a.i./ha. Applications were made at 7-day intervals. The last application occurred 7 days before harvest.

Commodity	Total Application Rate (g a.i./ha)	PHI (days)	Bupropion Residue Levels (ppm)							
			n	Min.	Max.	LAFT	HAFT	Median	Mean	SD
Head lettuce	1702	7	9	0.29	4.79	0.29	4.79	2.06	2.00	1.2
Leaf lettuce	1702	7	7	1.29	12.6	1.29	12.6	5.99	5.45	4.1
Celery	852	7	12	0.258	12.0	0.37	11.3	2.97	4.09	3.6
Spinach	852	7	12	0.712	18.1	0.789	16.7	6.78	7.18	5.1

All samples showed residues of BF 9 and BF 12 were each <0.01 ppm, with the following exception. For celery residues of BF 9 were 0.01-0.04 ppm (remaining 9 samples showed <0.01 ppm BF 9).

CROP FIELD TRIALS & RESIDUE DECLINE ON LYCHEES	PMRA # 21601000

Field trials were conducted in 2000 in the United States. Trials were conducted in NAFTA Growing Region 2 (3 trials). Applaud 70 WP was applied twice as foliar broadcast application for a total seasonal application rates of 3517-5166 g a.i./ha. The last application occurred 14 and 23 days before harvest.

Commodity	Total Application Rate (g a.i./ha)	PHI (days)	Bupropion Residue Levels (ppm)							
			n	Min.	Max.	LAFT	HAFT	Median	Mean	SD
Lychee	3517	23	4	0.041	0.296	0.098	0.192	0.141	0.145	0.09
	5166	14	2	0.107	0.243	-	-	-	0.175	-

CROP FIELD TRIALS & RESIDUE DECLINE ON OLIVE	PMRA # 21601371

Field trials were conducted in 2004 in the United States. Trials were conducted in NAFTA Growing Region 10 (4 trials). Applaud 70WP was applied twice as foliar broadcast applications at a rate of 2365-2832 g a.i./ha/application for a seasonal application rate of 4740-6051 g a.i./ha. The last application occurred approximately 21-23 days before harvest.

Commodity	Total Application Rate (g a.i./ha)	PHI (days)	Bupropion Residue Levels (ppm)							
			n	Min.	Max.	LAFT	HAFT	Median	Mean	SD
Olive	8740-8974	28–29	4	0.813	1.037	0.887	1.506	1.098	1.073	0.301

CROP FIELD TRIALS & RESIDUE DECLINE ON PAPAYA	PMRA # 2180/2068

Field trials were conducted in 2006 in the United States. Trials were conducted in NAFTA Growing Region 5 (3 trials). Applaud 70 WP was applied five times as foliar broadcast application at a rate of 817-867 g a.i./ha/application for a seasonal application rate of 2085-2230 g a.i./ha. The last application occurred 2–3 days before harvest.

Commodity	Total Application Rate (g a.i./ha)	PHI (days)	Bupropion Residue Levels (ppm)							
			n	Min.	Max.	LAFT	HAFT	Median	Mean	SD
Papaya	2085–2230	2–3	6	0.83	0.68	0.70	0.67	0.62	0.59	0.09

CROP FIELD TRIALS & RESIDUE DECLINE ON TREE NUTS CG 14-11 (ALMONDS, PECANS)	PMRA # 2180/2179, 2180/2187

Field trials were conducted in 1996 in the United States for almonds. Trials were conducted in NAFTA Growing Region 10 (6 trials). Applaud 70 WP was applied once as a foliar broadcast application at a rate of 2240 g a.i./ha. The last application occurred 70-90 days before harvest.

Field trials were conducted in 2009 in the United States for pecans. Trials were conducted in NAFTA Growing Regions 2 (2 trials), 4 (1 trial), 6 (1 trial), and 8 (1 trial). Applaud 70 WP was applied once as a foliar broadcast application at a rate of 1680 g a.i./ha. The last application occurred 60 days before harvest.

Commodity	Total Application Rate (g a.i./ha)	PHI (days)	Bupropion Residue Levels (ppm)							
			n	Min.	Max.	LAFT	HAFT	Median	Mean	SD
Almonds	2240	70-90	12	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	-
Pecans	1680	60	10	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	-

Residues of BP 9 and BP 12 were each less than LOQ in almonds (<0.05 ppm) and in pecans (<0.01 ppm).

CROP FIELD TRIALS & RESIDUE DECLINE ON FRUITING VEGETABLES CG 8-09 (TOMATOES, PEPPERS)	PMRA # 2180/272, 2180/275

Field trials were conducted in 2007 in the United States for tomatoes. Trials were conducted in NAFTA Growing Regions 2 (2 trials), 3 (2 trials), 5 (1 trial), and 10 (5 trials). Course 80 SC was applied twice as foliar broadcast applications at rates of 815–869 g a.i./ha/application for a seasonal application rates of 840-929 g a.i./ha. Applications were made at 24–30-day intervals. The last application occurred 1day before harvest.

Field trials were conducted in 2008 in the United States. Trials were conducted in NAFTA Growing Regions 2 (2 trials), 3 (2 trials), 5 (1 trial), 6 (1 trial), and 10 (2 trials) for bell peppers, and in NAFTA Growing Regions 3 (1 trial), 6 (1 trial), and 10 (1 trial) for non-bell peppers. Course 80 SC was applied twice as foliar broadcast application at a rate of 818–847 g a.i./ha/application for a seasonal application rate of 836-889 g a.i./ha. Applications were made at 6-8-day intervals. The last application occurred 1 day before harvest.

Commodity	Total Application Rate (g a.i./ha)	PHI (days)	Bapelticon Residue Levels (ppm)							
			n	Min.	Max.	LAFT	HAFT	Median	Mean	SD
Tomato	840-870	1	24	<0.03	0.74	0.03	0.47	0.098	0.134	0.13
Bell Pepper	830-880	1	10	0.13	0.56	0.13	0.46	0.21	0.28	0.20
Non-Bell Pepper	830-880	1	6	0.10	1.10	0.10	0.9	0.69	0.56	0.37

CROP FIELD TRIALS & RESIDUE DECLINE ON CUCUMBER (CG 9 (CUCUMBER, MUSKMELON, SUMMER SQUASH))	PMRA # 2180322, 2180327

Field trials were conducted in 1994 in the United States for muskmelons. Trials were conducted in NAFTA Growing Regions 2 (3 trials), 7 (3 trials), 8 (2 trials), 9 (1 trial), and 10 (3 trials). Applisad 80 SC was applied four times as foliar broadcast applications at a nominal rate of 820 g a.i./ha/application for a seasonal application rate of 1702 g a.i./ha. The last application occurred 7 days before harvest.

Field trials were conducted in 1994 in the United States for summer squash. Trials were conducted in NAFTA Growing Regions 1 (1 trial), 2 (3 trials), 3 (3 trials), 7 (2 trials), 8 (2 trials), and 10 (2 trials). Applisad 80 SC was applied four times as foliar broadcast applications at a nominal rate of 820 g a.i./ha/application for a seasonal application rate of 1702 g a.i./ha. The last application occurred 7 days before harvest.

Field trials were conducted in 1994 in the United States for cucumbers. Trials were conducted in NAFTA Growing Regions 2 (6 trials), 3 (2 trials), 7 (6 trials), 8 (2 trials), and 10 (5 trials). Applisad 80 SC was applied four times as foliar broadcast application at a nominal rate of 820 g a.i./ha/application for a seasonal application rate of 1702 g a.i./ha. The last application occurred 7 days before harvest.

Commodity	Total Application Rate (g a.i./ha)	PHI (days)	Bapelticon Residue Levels (ppm)							
			n	Min.	Max.	LAFT	HAFT	Median	Mean	SD
Cucumber	1702	7	17	<0.01	0.28	<0.01	0.28	0.032	0.086	0.088
Muskmelon	1702	7	12	0.17	0.61	0.17	0.61	0.35	0.33	0.18
Summer squash	1702	7	12	0.02	0.11	0.02	0.11	0.04	0.04	0.02

Residues of BF 9 and BF 12 were each <0.01 ppm, except for two samples of muskmelon where residues were each 0.01 ppm for BF 12.

CROP FIELD TRIALS & RESIDUE DECLINE ON TEA	PMRA # 2180267

Three field trials were conducted in 1981 and in 1996 in Japan. Bapelticon formulated as 240 SC formulation was applied twice as foliar broadcast applications at a rate of 2500 g ai/ha/application for a seasonal application rate of 5000 g ai/ha. The last application occurred 14 days before harvest.

Commodity	Total Application Rate (g a.i./ha)	PHI (days)	Bapelticon Residue Levels (ppm)							
			n	Min.	Max.	LAFT	HAFT	Median	Mean	SD
Crude Tea	5000	14	6	6.50	10.20	7.12	9.94	8.24	8.40	1.5

GREENHOUSE TRIALS & RESIDUE DECLINE ON CUCUMBERS	PMRA # 2179963

Greenhouse trials were conducted in 2007 in Canada and in the United States. Trials were conducted in NAFTA Growing Regions 5 (2 trials) and 8 (1 trial). Courier SC was applied two or three times as foliar broadcast sprays at rates of 130-436 g a.i./ha/application for a seasonal application rate of 842-859 g a.i./ha. Applications were made at 1-7-day intervals. The last application occurred 1day before harvest.

One residue decline trial was conducted in 2007 in Canada in NAFTA Growing Region 5 (1 trial). Courier SC was *applied twice as a foliar application for a seasonal application rate of 857 g a.i./ha. It is noted that the location of the trials is not critical since greenhouses have controlled environments.*

Commodity	Total Application Rate (g a.i./ha)	PHI (days)	Buprofezin Residue Levels (ppm)							
			n1	Min.	Max.	LAFT	HAFT	Median	Mean	SD
Greenhouse Cucumbers	842-859	1	6	<0.01	0.11	<0.05	0.09	0.065	0.07	0.03
	857	0	2	0.07	0.07	0.07	0.07	-	0.07	-
		1	2	<0.05	<0.05	<0.05	<0.05	-	<0.05	-
		3	2	<0.05	<0.05	<0.05	<0.05	-	<0.05	-
		6	2	<0.05	<0.05	<0.05	<0.05	-	<0.05	-
		8	2	<0.05	<0.05	<0.05	<0.05	-	<0.05	-

GREENHOUSE CROP FIELD TRIALS & RESIDUE DECLINE ON TOMATOES	PMRA # 2179974

Greenhouse trials were conducted in 2001 in the United States. Trials were conducted in NAFTA Growing Regions 4 (1 trial) and 6 (1 trial). Applaud 70 WP was applied twice as foliar directed sprays at a nominal rate of 392 g a.i./ha/application for actual application rates of 776-790 g a.i./ha per crop cycle. Applications were made at 4-6-day intervals. The last application occurred 1 day before harvest.

It is noted that the location of the trials is not critical since greenhouses have controlled environments.

Commodity	Total Application Rate (g a.i./ha)	PHI (days)	Buprofezin Residue Levels (ppm)							
			n1	Min.	Max.	LAFT	HAFT	Median	Mean	SD
Greenhouse Tomatoes	776-790	1	4	0.18	0.32	0.21	0.27	0.23	0.24	0.06

GREENHOUSE CROP FIELD TRIALS & RESIDUE DECLINE ON PEPPERS	PMRA # 2179970, 2179971

Greenhouse trials were conducted in 2001 and in 2002 in the EU. Trials were conducted in the UK (3 trials), S. France (3 trials), S. Spain (3 trials), and Greece (1 trial). Buprofezin 25 SC and 25 WP were applied three times as foliar directed sprays at a nominal rate of 250 g a.i./ha/application for a total rate of 750 g a.i./ha per crop cycle. Applications were made at 6-8-day intervals. The last application occurred 3 and 7 days before harvest.

Residue decline trials were also conducted, as described below. It is noted that the location of the trials is not critical since greenhouses have controlled environments.

Commodity	Total Application Rate (g a.i./ha)	PHI (days)	Buprofezin Residue Levels (ppm)							
			n1	Min.	Max.	LAFT	HAFT	Median	Mean	SD
Greenhouse Peppers	750	0	6	0.1	0.7	-	-	0.185	0.312	0.26
		3	10	0.08	0.48	-	-	0.19	0.241	0.15
		7	10	0.04	0.23	-	-	0.125	0.125	0.07
		10	6	0.03	0.14	-	-	0.072	0.072	0.05

Residues of BF 9 and BF 12 were each <0.01 ppm in every sample.

n1 = number of samples analysed.

PROCESSED FOOD AND FEED - APPLE	PMRA # 2180395
Test Site	One trial in NAFTA Growing Region 1.
Treatment	Broadcast foliar applications
Rate	3360 g a.i./ha
End-use product/formulation	*Applaud 70WP*
Preharvest interval	14 days
Processed Commodity	Average Processing Factor
Apple Juice	0.6x
PROCESSED FOOD AND FEED - PLUM	**PMRA # 2180394**
Test Site	One trial in NAFTA Growing Region 10.
Treatment	Broadcast foliar applications
Rate	3536-3575 g a.i./ha
End-use product/formulation	Applaud 70WP
Preharvest interval	14 days
Processed Commodity	Average Processing Factor
Dried Plum	2.1x
PROCESSED FOOD AND FEED - GRAPES	**PMRA # 2180402**
Test Site	One trial in NAFTA Growing Region 10.
Treatment	Broadcast foliar applications
Rate	5600 g a.i./ha
End-use product/formulation	Applaud 70WP
Preharvest interval	30 days
Processed Commodity	Average Processing Factor
Juice	0.1x
Raisins	2.4x
PROCESSED FOOD AND FEED - ORANGE	**PMRA # 2180406**
Test Site	One trial in NAFTA Growing Region 10.
Treatment	Broadcast foliar applications
Rate	22,400 g a.i./ha
End-use product/formulation	Applaud 70DF
Preharvest interval	3 days
Processed Commodity	Average Processing Factor
Juice	0.006x
Oil	30x
PROCESSED FOOD AND FEED - TOMATOES	**PMRA # 2180401**
Test Site	One trial in NAFTA Growing Region 10.
Treatment	Broadcast foliar applications
Rate	4166 g a.i./ha
End-use product/formulation	Applaud 40SC
Preharvest interval	7 days
Processed Commodity	Average Processing Factor
Juice	0.1x
Puree	0.7x
Paste	1.3x
PROCESSED FOOD AND FEED - COFFEE	**PMRA # 2180374**

Test Site	One trial in NAFTA Growing Region 13.
Treatment	Broadcast foliar applications
Rate	4514-5712 g a.i./ha
End-use product/formulation	Applaud 70WP
Preharvest interval	0 day
Processed Commodity	Average Processing Factor
Roasted bean	0.3x
Freeze dried coffee	0.2x
PROCESSED FOOD AND FEED - COTTONSEED	PMRA # 2180403
Test Site	One trial in NAFTA Growing Region 10.
Treatment	Broadcast foliar applications
Rate	8512 g a.i./ha
End-use product/formulation	Applaud 70WP
Preharvest interval	14 days
Processed Commodity	Average Processing Factor
Refined oil	0.3x
PROCESSED FOOD AND FEED - OLIVES	PMRA # 2180371
Test Site	One trial in NAFTA Growing Region 10.
Treatment	Broadcast foliar applications
Rate	24195 g a.i./ha
End-use product/formulation	Applaud 70WP
Preharvest interval	21 days
Processed Commodity	Average Processing Factor
Olive oil	3.1x

Table 13 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

PLANT STUDIES		
RESIDUE DEFINITION FOR ENFORCEMENT Primary crops Rotational crops		Buprofezin NA
RESIDUE DEFINITION FOR RISK ASSESSMENT Primary crops Rotational crops		Buprofezin NA
METABOLIC PROFILE IN DIVERSE CROPS		The profile in four diverse crops was investigated. Similar in lettuce, lemon, tomato, and cottonseed.
DIETARY RISK FROM FOOD		
Refined chronic non-cancer dietary exposure analysis ADI = 0.01 mg/kg bw/day No exposure from drinking water	POPULATION	ESTIMATED RISK % of ACCEPTABLE DAILY INTAKE (ADI)
		Food Alone
	All infants < 1 year	2.5
	Children 1–2 years	7.3

	Children 3 to 5 years	5.1
	Children 6–12 years	3.1
	Youth 13–19 years	1.7
	Adults 20–49 years	2.6
	Adults 50+ years	3.5
	Females 13-49 years	2.7
	Total population	3.1
Basic acute dietary exposure analysis, 95th percentile ARfD = 0.5 mg/kg bw No exposure from drinking water.	POPULATION	ESTIMATED RISK % of ACUTE REFERENCE DOSE (ARfD)
		Food Alone
	All infants < 1 year	32.4
	Children 1–2 years	48.1
	Children 3 to 5 years	37.4
	Children 6–12 years	20.0
	Youth 13–19 years	12.7
	Adults 20–49 years	12.4
	Adults 50+ years	13.3
	Females 13-49 years	12.7
	Total population	17.9
Refined cancer dietary exposure analysis q_1^* = 2.3 × 10-3 (mg/kg bw/day)-1 No exposure from drinking water.	POPULATION	ESTIMATED LIFETIME CANCER RISK
		Food Alone
	Total population	7 × 10-7

Table 14 Effects on terrestrial organisms

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA#
Invertebrates					
Bees	48h-Oral	buprofezin	>163.5 ug a .i./bee		DER: 2179666
	72h-Contact	buprofezin	>200 ug a .i./bee	Relatively non-	DER:

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA#
				toxic	2179525 Study: 2179665
	Acute - Tier 1 brood study	Buprofezin 25WP	Reproductive LD_{50}>2.67 g Buprofezin 25WP/hive (0.67 g a.i./hive) – cannot relate this to field application rate	No effects on brood when adult worker bees are dosed with 2.67 g Buprofezin 25WP/hive (0.67 g a.i./hive)	PMRA DER: 2309615 Study: 2179667
	Not guideline study; comparative study examining reproductive effects between several IGRs	Applaud SC (250 g a.i./L)		Reproductive effects (no. males produced) were noted at 79 (41-153) mg a.i./L via pollen exposure, maximum single EU field rate = 1000 g a.i./ha so assuming this is rate used in study, results can be considered approximately equivalent to the maximum proposed application rate of 686 g a.i./ha for greenhouse ornamentals	PMRA 2321899 Mommaerts et al (2006)
Predatory arthropod *Typhlodromus*	14-d Contact		LR_{50} > 100 kg a.i./ha	n/a	PMRA DER: 2309616
	14-d		LR_{50} > 100 kg	n/a	

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA#
pyri	reproductive		a.i./ha		Study: 2179668
Phytoseiulus persimilis	8-day Contact	Applaud 25SC	Could not be determined, study deemed not reliable	n/a	
Parasitic arthropod *Encarsia formosa*	24h-Contact		LR_{50} > 42.5 kg a.i./ha	n/a	
	14d-reproductive		ER_{50}> 42.5 kg a.i./ha	n/a	
Predatory mite	Field study		Could not be determined, study deemed scientifically unsound	n/a	PMRA DER: 2309616 Study: 2179669

[a] Atkins et al. (1981) for bees and US EPA classification for others, where applicable.

Table 15 Effects on Aquatic Organisms

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA#
Freshwater species					
Daphnia magna	48h-Acute	Buprofezin	EC_{50}>0.42 mg a.i./L Acute 48h LC_{50} = 0.84 mg a.i./L	Cannot classify as LC_{50} determined only as a greater than value Highly toxic	2179512 2179514
	21-d chronic		NOEC = 0.080 mg a.i./L LOEC= 0.12 mg a.i./L	Most sensitive endpoint was reproduction	2179529
Rainbow trout	96h-Acute		LC_{50} >0.33 mg a.i./L NOEC = 0.33 mg a.i./L	Cannot classify as LC_{50} determined only as a greater than	2179517

				value	
Bluegill Sunfish	96h-Acute		LC_{50} >0.33 mg a.i./L NOEC = 0.33 mg a.i./L	Highly toxic	2179516

Table 16 Fate and Behaviour in the Environment

Property	Result	Comment
Vapour pressure at 25°C	4.2×10^{-5} Pa at 20°C 1.7×10^{-4} Pa at 30°C	low volatility PMRA 2200497 (CES review) PMRA 2322049 - calculations
Henry's law constant at 25°C K = vp (atm) × molecular weight (g/mol)/solubility (mg/L)	1.33×10^{-4} atm m^3 / mole	Low potential to volatilize from water or moist soil
Partition coefficient, $H=C_{air}/C_{water}$	$H = 5.42 \times 10^{-3}$ $1/H = 1.84 \times 10^{2}$	Non-volatile from a water surface (EPA 1995)
Ultraviolet (UV) / visible spectrum	acidic: 227 nm neutral: 203 and 243 nm basic :212 and 243 nm	no UV maxima at environmentally relevant wavelengths, significant shift of UV vis max abs. indicates protonation in acidic solutions (that is, pH of solution has an effect on UV/VIS spectrum of buprofezin) (PMRA 2179551)
Solubility in water at 25°C	Solubility pH 7: 0.382 mg/L	PMRA 2200497 (CES review) sparingly soluble to low solubility in water
Solubility (g/L) in organic solvents at °C	MeOH: 87 g/L n-hexane: 20 g/L ethyl acetate: 220 g/L acetone; 240 g/L toluene: 320 g/L chloroform: 529 g/L	PMRA 2200497 (CES review)
n-Octanol/water partition coefficient (Kow)	pH 7: log K_{ow} = 4.31	PMRA 2200497 (CES review) Potential for bioaccumulation under environmentally relevant pH levels
Dissociation constant	does not ionize or dissociate	

Property	Value	Major Transformation products	Comments	PMRA#
Abiotic transformation				
Hydrolysis	pH 5 DT_{50} = 51 days pH 7 =	BF-25 N-[[(1,1-dimethylethyl)amino]thioxomethyl]-	Formed at pH 5; max 19.0% AR at	DER: 2179485study: 2179648

	stable pH 9 = stable	N-(1-methylethyl)-N-phenylurea 	30DAT	
Aqueous photolysis	Half-life = 38 days	no major transformation products identified	40°N mid-summer	DER: PMRA 2179491
Phototransformation on soil	*Apparent* half-life = 39 days	no major transformation products identified	that the study authors indicated the possibility that volatilisation from soil was the major dissipation pathway in the study and that buprofezin may be stable to photolysis in soil and not expected to undergo soil photolysis.	DER: 2179490 Study: 2179650
Phototransformation in air	Half-life = 2.4 hours	Estimate done using EPISuite, cannot provide information on potential transformation products	not expected to undergo long range atmospheric transport (AopWin v1.91 EPA	2209182

			EPISuite).	
Biotransformation				
Biotransformation in aerobic soil	Sandy loam: DT_{50} = 26.3 days DT_{90} = 98.2 days Sandy clay loam: DT_{50} = 69.6 days DT_{90} = 305 days	no major transformation products identified	slightly to moderately persistent (Goring et al 1975)	DER: 2179487 Study: 2179653
Mobility				
Adsorption / desorption in soil	Freundlich K_{ads} (mg/g) sand = 11 clay loam = 85 sandy loam=69; 87; 90 loamy sand = 70 silty clay loam=277 $K_{oc\text{-}ads}$ 2100-4800	no major transformation products identified	slightly mobile	DER: 2179492 Study: 2179657
Aged Soil leaching	loamy sand: 0-5 cm segment: 98-106% AR sandly loam: 0-8 cm segment: 65-85% AR	classified by EPA as supplemental (in part) as transformation products were not identified	not mobile	DER: 2179481 Study: 2179658

Aerobic water/sediment	Total system (geometric mean for 2 systems; clay and sand) = 49 days	Tests conducted at 20°C, kinetics follow SFO	Slightly persistent – taken from EFSA review	PMRA 2321948
	Sandy: Total system DT_{50} = 47 days Silty Clay: Total system DT_{50} = 51 days			
Anaerobic aquatic	Stable: half-life 1200 days	no major transformation products identified		PMRA 2179656
Bioaccumulation	BCF for: Fillet = 86X Viscera = 86X Whole fish tissue = 537X	BF-12 and 2 major unidentified degradates (Metabolites 1 and 2)	During the 7 day depuration, 92% - 99% of the accumulated residues during the 14 day exposure period were eliminated from fish tissue	DER:2179527 study: 2179684

Table 17 Toxicity to Non-Target Species

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA#
Invertebrates					
Bees	48h-Oral	buprofezin	>163.5 ug a .i./bee		DER: 2179666
	72h-Contact	buprofezin	>200 ug a .i./bee	Relatively non-toxic	DER: 2179525 Study:

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA#
					2179665
	Acute - Tier 1 brood study	Buprofezin 25WP	Reproductive LD_{50}>2.67 g Buprofezin 25WP/hive (0.67 g a.i./hive) – cannot relate this to field application rate	No effects on brood when adult worker bees are dosed with 2.67 g Buprofezin 25WP/hive (0.67 g a.i./hive)	PMRA DER 2309615 Study 2179667
	Not guideline study; comparaitive study examining reproductive effects between several IGRs	Applaud SC (250 g a.i./L)		Reproductive effects (no males produced) were noted at 79(41-153) mg a.i/L via pollen exposure, maximum single EU field rate = 1000 g a.i./ha so assuming this is rate used in study, results can be considered approximately equivalent to the maximum proposed applicationrate of 686 g a.i./h for greenhouse ornamental.	PMRA 2321899 Mommaerts et al (2006)
Predatory arthropod *Typhlodromus pyri*	14-d Contact		LR_{50} > 100 kg a.i./ha	n/a	PMRA DER 2309616 Study 2179668
	14-d reproductive		LR_{50} > 100 kg a.i./ha	n/a	
Phytoseiulus persimilis	8-day Contact	Applaud 25SC	Could not be determined, study deemed not reliable	n/a	
Parasitic arthropod *Encarsia*	24h-Contact		LR_{50} > 42.5 kg a.i./ha	n/a	
	14d-		ER_{50}> 42.5 kg	n/a	

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity*	PMRA#
formosa	reproductive		a.i./ha		
Predatory mite	Field study		Could not be determined, study deemed scientifically unsound	n/a	PMRA DER 2809616 Study 2179669
Green lacewing (*Chrysoperla carnea*)	No endpoint available, information is taken from EFSA Journal 2010 review of buprofezin. Low hazard at application rates of 0.188 – 3.0 kg a.i./ha			Low hazard	PMRA 2321948

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity*	PMRA#
Freshwater species					
Daphnia magna	48h-Acute	buprofezin	EC_{50}>0.42 mg a.i./L Acute 48h LC_{50} = 0.84 mg a.i./L	Cannot classify as EC_{50} determined only as a greater than value Highly toxic	2179512 2179514
	21-d chronic		NOEC = 0.080 mg a.i./L LOEC= 0.12 mg a.i./L	Most sensitive endpoint was reproduction	2179529
Rainbow trout	96h-Acute		LC_{50} >0.33 mg a.i./L NOEC = 0.33 mg a.i./L	Cannot classify as EC_{50} determined only as a greater than value	2179517
Bluegill Sunfish	96h-Acute		LC_{50} >0.33 mg a.i./L NOEC = 0.33 mg a.i./L	Highly toxic	2179516

* Atkins et al. (1981) for bees and US EPA classification for others, where applicable

Table 10 Screening Level Risk Assessment on Non-Target Species

Organism (PMRA)	Exposure and Endpoint value	Uncertainty Factor Applied	EEC	Risk Quotient	Risk
Invertebrates					
Bee (2179666, 2179925, 2309615)	48 h – oral >163.5 ug a i./bee (28.4 kg a i./ha)	1	0.686 kg a i./ha	0.026	no
	72h-Contact >200 ug a i./bee (480 kg a i./ha)	1		0.001	no
	21 day Tier 1 brood study: Reproductive LD_{50}>2.67 g Buprofezin 25WP/hive (0.67 g a i./hive)	n/a		Cannot calculate as the exposure to hives cannot be expressed in terms of an application rate	n/a
Predatory arthropod *Typhlodromus pyri* (2309616)	14-d Contact LR_{50} > 100 kg a i./ha	1		0.0069	no
	14-d reproductive LR_{50} > 100 kg a i./ha	n/a		0.0069	
Parasitic arthropod *Encarsia formosa* (2309616)	24h-Contact LR_{50} > 42.5 kg a i./ha	1		0.016	
	14d-reproductive ER_{50}> 42.5 kg a i./ha	n/a		0.016	
Green lacewing *(Chrysoperla carnea)*	No endpoint available, information is taken from EFSA review (EFSA Journal 2010; PMRA 2321948)			Low hazard at application rates of 0.188 – 3.0 kg a i./ha	Not expected as the maximum application rate of 0.686 kg a i./ha

Organism (PMRA #)	Exposure and Endpoint value	Uncertainty Factor Applied	EEC	Risk Quotient	Risk
Freshwater species					
Daphnia magna (2179512)	48-hr EC_{50}=0.62 mg a.i./L		Cannot estimate aquatic EEC at this time	Cannot assess without aquatic EEC	n/a
(2179514)	Acute 48h LC_{50} = 0.84 mg a.i./L				
(2179529)	21-d chronic NOEC = 0.080 mg a.i./L LOEC= 0.12 mg a.i./L				
Rainbow trout (2179517)	96h-Acute LC_{50} >0.33 mg a.i./L NOEC = 0.33 mg a.i./L				
Bluegill Sunfish (2179516)	96h-Acute LC_{50} >0.33 mg a.i./L NOEC = 0.33 mg a.i./L				

Appendix II Supplemental Maximum Residue Limit Information—International Situation and Trade Implications

Table 1 compares the MRLs proposed for bupropion in Canada with corresponding American tolerances and Codex MRLs[*]. American tolerances are listed in the Electronic Code of Federal Regulations, 40 CFR Part 180, by pesticide. A listing of established Codex MRLs is available on the Codex Alimentarius Pesticide Residues in Food website, by pesticide or commodity.

Table 1 Comparison of Canadian MRLs, American Tolerances and Codex MRLs (where different)

Food Commodity	Canadian MRL (ppm)	American Tolerance (ppm)	Codex MRL (ppm)
Bananas	0.3	0.2	0.3
Low growing berry (CSG 13-07G)	3	2.5	3 (strawberry)
Orange subgroup (CSG 10A)	4	2.5 (CG 10)	1 (CG 10)
Citrus Oil	80	80	Not Established
Apples, crabapples, loquats, mayhaws, quinces	3	3 (CG 11-09, except pear and Asian pear)	3 (apple)
Pears and Asian pears	6	6 (Pear and Asian pear)	6 (pear)
Cherry subgroup (CGS 12-09A) & Plum subgroup (CGS 12-09C)	2	1.9 (CG 12-09, except peach and apricot)	2 (cherries and plums)
Peach subgroup (CSG 12-09B)	9	9 (peach and apricot)	9 (peach and nectarine)
Grapes	1	2.5	1
Raisins	2	Not Established	2
Leafy Vegetables (except Brassica) (CG 4)	35	35 (CG 4, except head lettuce and radicchio) 6 (head lettuce and radicchio)	Not Established
Olives	5	3.5	5
Cucurbit Vegetables (CG 9)	0.7	0.5	0.7
Tea	30	20	30

[*] The Codex Alimentarius Commission is an international organization under the auspices of the United Nations that develops international food standards, including MRLs.

MRLs may vary from one country to another for a number of reasons, including differences in pesticide use patterns and the locations of the field crop trials used to generate residue chemistry data.

Under the North American Free Trade Agreement (NAFTA), Canada, the United States and Mexico are committed to resolving MRL discrepancies to the broadest extent possible. Harmonization will standardize the protection of human health across North America and promote the free trade of safe food products. Until harmonization is achieved, the Canadian MRLs specified in this document are necessary. The differences in MRLs outlined above are not expected to impact businesses negatively or adversely affect international competitiveness of Canadian firms or to negatively affect any regions of Canada.

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Document Number	Reference
2314222	2013, Buprofezin Manufacturing Method [CBI removed] DACO 2_11, DACO: 2.11
2179537	1993, Buprofezin Technical Product Chemistry: Product Identify and Composition, DACO: 2.11.1,2.11.2,2.11.3,2.11.4
2179546	2007, Content Analysis of Buprofezin Technical Product, DACO: 2.13.2,2.13.3
2314206	2003, Validation of Analytical Methods and Profile of Representative Batches ofBuprofezin Technical, DACO: 2.13,2.13.1,2.13.2
2314223	2011, Content Analysis Of Buprofezin Technical Product [CBI Removed] , DACO: 2.13,2.13.1,2.13.2,2.13.3
2179539	1993, Buprofezin Technical Product Chemistry: Product Identify and Composition, DACO: 2.11.1,2.11.2,2.11.3,2.11.4
2179545	2004, Buprofezin Technical Preliminary Analysis
2412066	2014, Structural Identification and Purity Analysis for Buprofezin Standard (Lot No. 9AD0022Z), DACO: 2.13.2
2412067	2014, Structural Identification, Purity Analysis and Stability Study for Buprofezin Impurities: [CBI removed]
2442586	2014, Clarification Response For Submission 2012-1419 (Nichino Buprofezin Technical), DACO: 2.13.2
2442585	2007, Continuation Of Identity For Impurities In Buprofezin Technical By [CBI removed], DACO: 2.13.2
2442587	2007, Continuation Of Identity For Impurities In Buprofezin Technical By [CBI removed], DACO: 2.13.2
2442589	2009, Structural Identification and Purity Analysis for Buprofezin Standard (Lot No. 9AD0022Z), DACO: 2.13.2
2442590	2011, Structural Identification, Purity Analysis and Stability Study for Buprofezin Impurities: [CBI removed]
2179548	1993, Buprofezin Technical 2-Tert-Butylimino-3-Isopropyl-5-Phenylperhydro-1,3,5-Thiadiazin-4-One as Active Ingredient EPA File Symbol (To Be Assigned)
2179541	2009, Analytical Method Validation and Physico-Chemical Testing on Buprofezin, DACO: 2.13.1

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3.0 Environment

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B. Additional Information Considered

i) Published Information

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